"A STUDY ON HISTOPATHOLOGICAL SPECTRUM OF LESIONS IN URINARY BLADDER BIOPSIES"

By

Dr. S. SUSMITHA$_{MBBS}$

DISSERTATION SUBMITTED TO THE
BLDE UNIVERSITY'S, VIJAYAPURA, KARNATAKA

In partial fulfillment of the requirements for the award of the degree of

DOCTOR OF MEDICINE

IN

PATHOLOGY

UNDER THE GUIDANCE OF

Dr.GIRIJA S PATIL $_{MD}$
ASSOCIATE PROFFESOR,
DEPARTMENT OF PATHOLOGY

&

CO GUIDANCE OF

Dr. SIDDANAGOUDA. B. PATIL $_{MS, M.ch}$
PROFESSOR AND HEAD,
DEPARTMENT OF UROLOGY

BLDE UNIVERSITY'S
SHRI B.M. PATIL MEDICAL COLLEGE,
HOSPITAL AND RESEARCH CENTER, VIJAYAPURA,
KARNATAKA
2018

B.L.D.E UNIVERSITY'S

SHRI B. M. PATIL MEDICAL COLLEGE, HOSPITAL & RESEARCH CENTRE, VIJAYAPURA

DECLARATION BY THE CANDIDATE

I hereby declare that this dissertation entitled **"A STUDY ON HISTOPATHOLOGICAL SPECTRUM OF LESIONS IN URINARY BLADDER BIOPSIES"**is a bonafide and genuine research work carriedout by me under the guidance of **Dr. GIRIJA S PATIL** AssociateProfessor,Department of Pathology and co-guidance of **Dr. S. B. PATIL** Professor and Head, Department of Urology. BLDEUniversity's Shri B.M.Patil Medical College, Hospital &Research Centre, Vijayapura, Karnataka.

Date: **Dr. S. SUSMITHA**

Place: Vijayapura

B.L.D.E UNIVERSITY'S

SHRI B. M. PATIL MEDICAL COLLEGE, HOSPITAL & RESEARCH CENTRE, VIJAYAPURA

CERTIFICATE BY THE GUIDE

This is to certify that the dissertation entitled **"A STUDY ON HISTOPATHOLOGICAL SPECTRUM OF LESIONS IN URINARY BLADDER BIOPSIES"** is a bonafide research work done by **Dr. S. SUSMITHA** in partial fulfillment of the requirements for the degree of **Doctor of Medicine (Pathology).**

Date:

Place: Vijayapura

Dr. GIRIJA S PATIL
Associate Professor,
Department of Pathology,
BLDEUniversity's
Shri B.M.Patil Medical College,
Hospital & Research Centre,
Vijayapura,Karnataka.

B.L.D.E UNIVERSITY'S

SHRI B. M. PATIL MEDICAL COLLEGE, HOSPITAL & RESEARCH CENTRE, VIJAYAPURA

CERTIFICATE BY THE CO-GUIDE

This is to certify that the dissertation entitled **"A STUDY ON HISTOPATHOLOGICAL SPECTRUM OF LESIONS IN URINARY BLADDER BIOPSIES"** is a bonafide research work done by**Dr. S. SUSMITHA**in partial fulfillment of the requirements for the degree of**Doctor of Medicine (Pathology).**

Date:

Place: Vijayapura

Dr. S. B. PATIL

Professor and HOD,
Department of Urology,
BLDEUniversity's
Shri B.M.Patil Medical College,
Hospital & Research Centre,
Vijayapura,Karnataka**.**

B.L.D.E UNIVERSITY'S

SHRI B. M. PATIL MEDICAL COLLEGE, HOSPITAL & RESEARCH CENTRE, VIJAYAPURA

ENDORSEMENT BY HEAD OF DEPARTMENT

This is to certify that the dissertation entitled **"A STUDY ON HISTOPATHOLOGICAL SPECTRUM OF LESIONS IN URINARY BLADDER BIOPSIES"** is a bonafide research work done by **Dr. S. SUSMITHA** in partial fulfillment of the requirements for the degree of **Doctor of Medicine (Pathology).**

Date:

Place: Vijayapura

Dr. B. R. YELIKAR
Professor and HOD,
Department of Pathology,
BLDEUniversity's
Shri B.M.Patil Medical College,
Hospital & Research Centre,
Vijayapura,Karnataka.

B.L.D.E UNIVERSITY'S

SHRI B. M. PATIL MEDICAL COLLEGE, HOSPITAL & RESEARCH CENTRE, VIJAYAPURA

ENDORSEMENT BY PRINCIPAL/ HEAD OF INSTITUTION

This is to certify that the dissertation entitled **"A STUDY ON HISTOPATHOLOGICAL SPECTRUM OF LESIONS IN URINARY BLADDER BIOPSIES"** is a bonafide research work done by **Dr. S. SUSMITHA** in partial fulfillment of the requirements for the degree of **Doctor of Medicine (Pathology).**

Date:

Place: Vijayapura

Dr. S. P. GUGGARIGOUDAR

Principal,

BLDEUniversity's
Shri B.M.Patil Medical College,
Hospital & Research Centre,
Vijayapura,Karnataka.

B.L.D.E UNIVERSITY'S

SHRI B. M. PATIL MEDICAL COLLEGE, HOSPITAL & RESEARCH CENTRE, VIJAYAPURA

COPYRIGHT

DECLARATION BY THE CANDIDATE

I hereby declare that the BLDE University, Karnataka shall have the rights topreserve, use and disseminate this dissertation / thesis in print or electronic format foracademic / research purpose.

Date: **Dr. S. SUSMITHA**

Place: Vijayapura

ACKNOWLEDGEMENT

This study has been accomplished with the grace of almighty. It gives me immense pleasure to express my heartfelt gratitude to allwho have helped me to explore the expanses of knowledge.

I would like to express my sincere and deepest gratitude to my teacher and guide ***Dr.Girija S Patil,*** *Associate Professor, Department of Pathology, for her encouragement and invaluable guidance throughout the course of my study. Her guidance helped me in all the time of research and writing of this thesis. I could not have imagined having a better advisor and mentor for my study.*

I am equally grateful to ***Dr. B.R. Yelikar,*** *Professor and H.O.D, Department of Pathology for his valuable suggestions, indispensable guidance given at all the steps of the study.*

I am thankful to ***Dr. S. B.Patil****, Professor and HOD, Department of Urology for hisvaluable suggestions and guidance in all the time of research and thesis writing.*

My heartful thanks to ***Dr.Vijayalaxmi S Patil****Asst. Prof,for her valuable guidance and support in all the time of research and thesis writing.*

I am also extremely fortunate to have a supportive staff in the department, who have advised and mentored me and made it possible for me to expeditethis dissertation. I am thankful to ***Dr. S.U. Arakeri****Prof,* ***Dr. S.B. Hippargi****Prof,****Dr.R.M.Potekar****Prof,****Dr. Mahesh H Karigoudar****Prof,* ***Dr. Prakash M. Patil****Assoc Prof,* ***Dr. Savitri M. Nerune****Asst prof,* ***Dr. Anita P Javalgi****Asst prof,* ***Dr. Mamatha K.*** *Asst Prof and* ***Dr.SnehaJawalkar****Asst Prof. for theirsupervision, assiduous concern and positive feedback at all steps of this work.*

My heartful thanks to ***Dr. Sathyashree K. V, Dr. Raga Sruthi****,* ***Dr. Lynda Rodrigues,*** *statistician* ***Vijayasorgavi****, my seniors, batchmates and juniors who have helped and encouraged me during my work.*

This work could not have been completed without the active support of thetechnical staff of Histopathology. Thank you ***Mrs.JessyJoseph****,****MrsVidya P, Mr. Mathad NB, Asst. Librarian (Mr. HarshavardhanSMaga)*** *and the non-teaching staff of Department of Pathology.*

*I am proud of many things in my life but nothing beats being mother of baby****Suhanya HN****, who has filled my life with love, laughter and happiness.*

I am deeply indebted to my parents ***Mrs. Sheela S Reddy*** *and* ***Dr.Shivanna Reddy G.N*** *who are two souls but worked with a single thought to bring me up in the path of perfection.*

I express my deep sense of gratitude for my grand parents ***Mrs. Rudramma*** *and* ***Late Dr.Lakshmana Reddy K. T*** *for their support throughout my life.*

Words are less to express my love and affection to mybetter half ***Dr.Hanumant V Nipanal*** *for being my strength and encouraging me at every step of this work.*

I am grateful for having prettiest and lovely sister ***Dr.Sampreeta S*** *who has helped me in various aspects that led me to successfully complete this dissertation work.*

Last but not the least, my sincere gratitude to all my study subjects whose cooperation has contributed to this study.

Date:

Dr. S. Susmitha

Place: Vijayapura

LIST OF ABBREVIATIONS USED

- TURBT - Transurethral resection of bladder tumor
- H&E - Hematoxylin and Eosin
- PUNLMP - Papillary Urothelial neoplasm of Low Malignant Potential
- NIPUC-LG - Non-invasive Papillary Urothelial Carcinoma, Low grade
- NIPUC-HG - Non-invasive Papillary Urothelial Carcinoma, High grade
- CIS - Carcinoma in situ
- IUC - Invasive Urothelial Carcinoma
- Fig - Figure
- AAR - Age Adjusted ratio
- WHO - World Health Organization
- ISUP - International Society of Urological pathology
- AJCC - American joint Committee of Cancer
- M:F - Male : Female
- IHC - Immunohistochemistry

ABSTRACT

INTRODUCTION:

Urinary bladder lesions constitute an important source of clinical signs and symptoms. Both non-neoplastic and neoplastic lesions are quite common. Neoplastic lesions are responsible for significant morbidity and mortality throughout the world. Urinary bladder cancer is 2nd most common cancer after prostate cancer in genitourinary system. Histopathologicalanalysis of cystoscopicbladder biopsy and Transurethral resection of the bladder tumor (TURBT) material are the mainstay for cancer diagnosis.

OBJECTIVE:

To describe the histopathological spectrum of urinary bladder lesions in TURBT and cystoscopic biopsies.

MATERIALS AND METHODOLOGY:

All cystoscopic bladder biopsies and TURBT specimens were included in the study. The specimens received in formalin were grossly examined and entire tissue was processed in all cases as per standard protocol. Multiple sections of 3-5 micron thickness were obtained and stained with H&E, followed by histopathologicalexamination to classify them into non – neoplastic & neoplasticlesions on light microscopy.

RESULTS:

Total 48 cases were studied, out of which 20 were cystoscopicbladder biopsies and 28were TURBT specimens.Among all cases, 20 were non-neoplastic lesions accounting to 41.67% and 28 were neoplastic lesions accounting to 58.33%. non-neoplastic lesions was predominantly comprised of chronic non-specific cystitis.

Among the 28 neoplastic lesions, urothelial carcinoma is the predominant type and was most commonly seen in age group of 51-80 years constituting 92.85%. These neoplastic lesions were more common among males (71.43%) with M:F ratio of 2.5:1. Invasive urothelial carcinoma was the predominant type followed by NIPUC-LG, PUNLMP and NIPUC-HGin the decreasing order of frequency**.**

CONCLUSION:

Urinary bladder lesions are heterogenous and are most commonly encountered by surgical pathologists. Bladder tumors are the commonest lesions and urothelial neoplasm being the predominant tumor type. Awareness regarding the various histological features of these lesions, their neoplastic potential, risk of recurrence and possible pitfalls can help pathologists for accurate diagnosis

KEYWORDS:

Cystoscopic bladder biopsy,Transurethral resection of the bladder tumor (TURBT), Urothelial neoplasm.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

INTRODUCTION

Urinary bladder lesions constitute an important source of clinical signs and symptoms, these are more disabling than lethal.[1]

Both non-neoplastic and neoplastic lesions are quite common. The non-neoplastic lesions include cystitis, malakoplakia, urachal lesions and tuberculosis.[2] Cystitis constitutes an important source of clinical signs and symptoms. Neoplastic lesions are responsible for significant morbidity and mortality throughout the world.[3]Both benign and malignant tumors occur, the later being more common. Majority of urinary tract tumors are epithelial in origin.[4]Urothelial carcinoma is the most common tumor of the bladder, representing 90% of the malignancies with this origin.[3]

Urinary bladder cancer is the 9thmost common cancer worldwide and second most common malignancy of genitourinary tract after prostate cancer. Bladder neoplasms accounts for 6% and 2% of the cancer incidence in the men and women respectively. Most cases present over the age of 50 years.[3]

As per Indian cancer registrar data, it is the 9th most common cancer accounting for 3.9% of all cancers.[2]

Cystoscopy is the primary diagnostic tool for patients who are suspected of having bladder tumors, which is useful in localizing bladder tumors and biopsies of the suspected lesions.[5]

Transurethral resection of the bladder tumor (TURBT) is a therapeutic procedure that allows assessment of the degree of differentiation, depth of tumor invasion, parameters useful for elaboration of diagnosis and prognosis.[3]

Thus the present study was conducted to describe the incidence of various lesions of urinary bladder, their clinical manifestation, and to classify them as non-neoplastic and neoplastic lesions.

AIMS AND OBJECTIVES

To describe the histopathological spectrum of urinary bladder lesions in TURBT and cystoscopic biopsies.

REVIEW OF LITERATURE

Urinary system is comprised of Kidneys, Ureters, Urinary Bladder and Urethra. The lower urinary tract is formed by renal pelvis, calyces, ureters, urinary bladder and urethra which acts as a storage organ of urine until it is excreted at convenient time.[6]The shape, size and position of urinary bladder keeps varying depending upon amount of urine and state of the adjacent viscera.[7]

EMBRYOLOGY

The cloaca is divided by developing urogenital septum into two parts, anterior urogenital sinus and posterior anal canal. The anterior urogenital sinus grows and further divides into three parts. The upper part being largest among all continues with allantois to form Urinary bladder. The allantois later forms anobliterated fibrous band and connects the apex of urinary bladder to umbilicus which is called median umbilical ligament. The middle part is called pelvic part of urogenital sinus. It is narrow and forms prostatic and membranous part of urethra. The terminal part forms the phallic part of urethra.[8]

The lining epithelium of urinary bladder is derived from endoderm of urogenital sinus. Whereas, the portion of epithelium in the area of trigone is derived from mesoderm as it is developed from the resorption of the mesonephric duct. The muscularis propria and serosa are derived from splanchnic mesoderm.[8]

The various congenital malformations encountered in urinary bladder are, [9]

- Agenesis,
- Exstrophy,
- Duplication and septation,
- Urachal cysts and its persistence and
- Diverticulum

GROSS ANATOMY

Urinary bladder is the hollow viscus which is situated in the anterior most aspect of the pelvic cavity.In its empty state, it resembles a three sided pyramid having a base, an apex, with two inferior surface and one superior surface.[7]It becomes ovoid shape when it is distended and can store up to 500ml of urine approximately.[10]

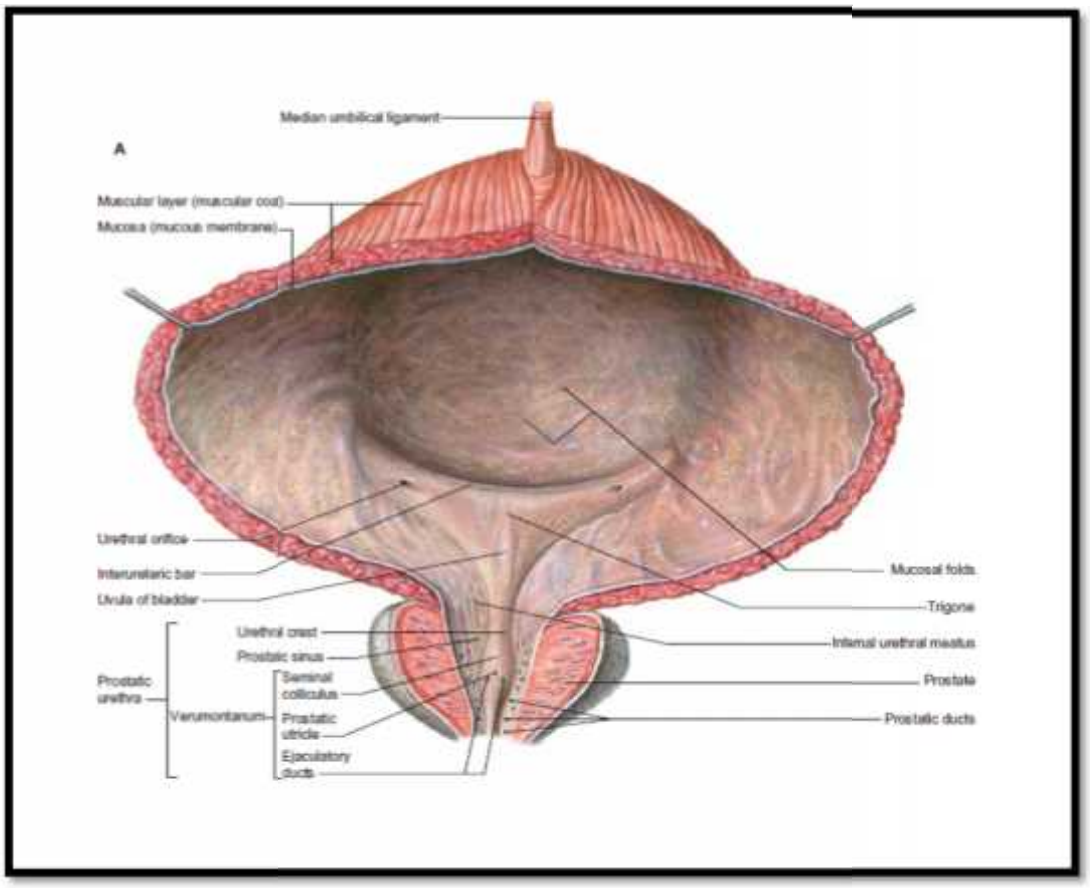


Fig 3.1: Coronal section of Urinary Bladder in males showing mucosal surface, trigone along with ureteric orifice and prostatic part of urethra. [7]

Relations

1. The Apex will be pointing towards the superior surface of pubic symphysis in both the sex. This is held in position by median umbilical ligament (urachus), which runs behind anterior abdominal wall.[7]

2. The Base of the bladder is inverted triangle in shape and is composed of trigone. To this trigone, the two ureters open at its each upper corner of the base, while the urethra opens at the lower corner.[7]

In males, base is posteriorly related to rectum. This is separated superiorly by rectovesical pouch, below by seminal vesical, vas deferens on either sides and Denonvillier's fascia. In females, posteriorly it is related to anterior wall of vagina.[7]

3. The Neck of the bladder is formed at a point where both of the inferior surfaces and base meets each other. It encases the origin of urethra and forms the inferior most part of the bladder. It is composed of smooth muscle bundle which are histologically and histochemicallydifferent from the detrusor muscle proper and thus considered as separate functional unit. This bladder neck is different in males and females.[7]

In males these smooth muscle bundles cover the bladder neck and pre-prostatic urethra. It has a rich supply of sympathetic noradrenergic receptors which helps to prevent retrograde ejaculation and does not seem to have any function in maintaining continence.[7]

In females, bladder neck is composed of small fasciculi and extends into urethral wall. This bladder neck rests above the pelvic floor and thus maintain the continence in normal young females. Whereas if this extends below the pelvic floor, the individuals will have stress incontinence which is commonly seen after parturition and with increasing age.[7]

4. The anterior surface is separated from Fascia transversalis by Retropubic space of Retzius containing fat.[7]

5. The two inferolateral surface rests on the pelvic diaphragm and are devoid of peritoneal covering.[7]

6. Superior surface, in males is completely covered by peritoneum and is related to sigmoid colon and terminal part of ileum. In females, the peritoneal covering is reflected posteriorly on the anterior wall of uterus at the level of internal os and this forms Vesico-uterine pouch.[7]

Blood supply

Urinary bladder gets its arterial blood supply from branches of internal iliac artery such as superior and inferior vesical artery. Superior vesical artery supplies superior and anterior surface of the bladder whereas the inferior vesical artery supplies the bladder base. The vessels which exits from the bladder forms the vesical venous plexus and empties into internal iliac veins.[11]

Lymphatic drainage

The lymphatics from lamina propria, muscularis and serosa forms channels on the bladder surface which runs beneath the fascia. The majority of the lymphatics drains into external iliac lymph nodes. Some portion of anterior and lateral lymphatics goes to obturator and internal iliac lymph nodes and part of base and trigone lymphatics drains into internal and common iliac lymph nodes.[10]

Nerve supply

Nerve supply to the bladder comes from pelvic plexus. It is formed by both efferent and afferent fibers composed of sympathetic and parasympathetic nerve bundles. Sympathetic fibers from the 1^{st} and 2^{nd} lumbar segments are motor to the vesicle sphincter and inhibitor to muscular wall. Parasympathetic fibers from pelvic splanchnic nerves (S2,3,4) are motor to the muscular wall and inhibitory to the vesicle sphincter muscle.[7]

HISTOLOGY OF URINARY BLADDER

The wall of urinary bladder is composed of four layers namely, Epithelium(urothelium), Lamina propria, Muscularis propria and adventitia or serosa.[11]The bladder is lined by specialized epithelium called urothelium, which was formerly called transitional epithelium. The mucosa in its contracted and empty state is thrown into folds and is lined by three to six layers of cells. While it is reduced to about three cell layerand flattens in its distended state, this is to accommodate the increase in the surface area.[6]

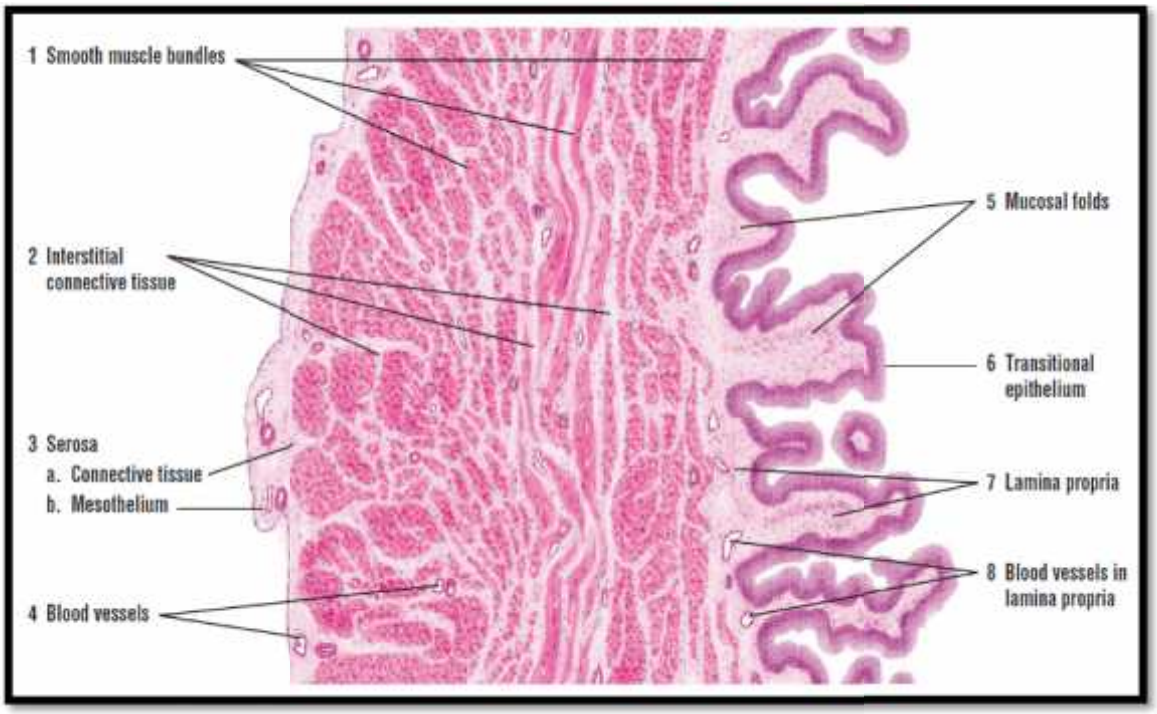


Fig*3.2: Transverse section of wall of urinary bladder, H&E, low magnification* [12]

These epithelial cells rests on a thin layer of basement membrane. The cells near to the basement membrane (basal cells) are cuboidal and are closely packed to each other.The intermediate layer cells are columnar with the nucleus arranged perpendicular to the basement membrane. The cells in the superficial layer are called Umbrella cells or dome cells, which are large oval with round nucleus and abundant

eosinophilic cytoplasm. These cells are capable of expanding when the bladder is distended.[6]

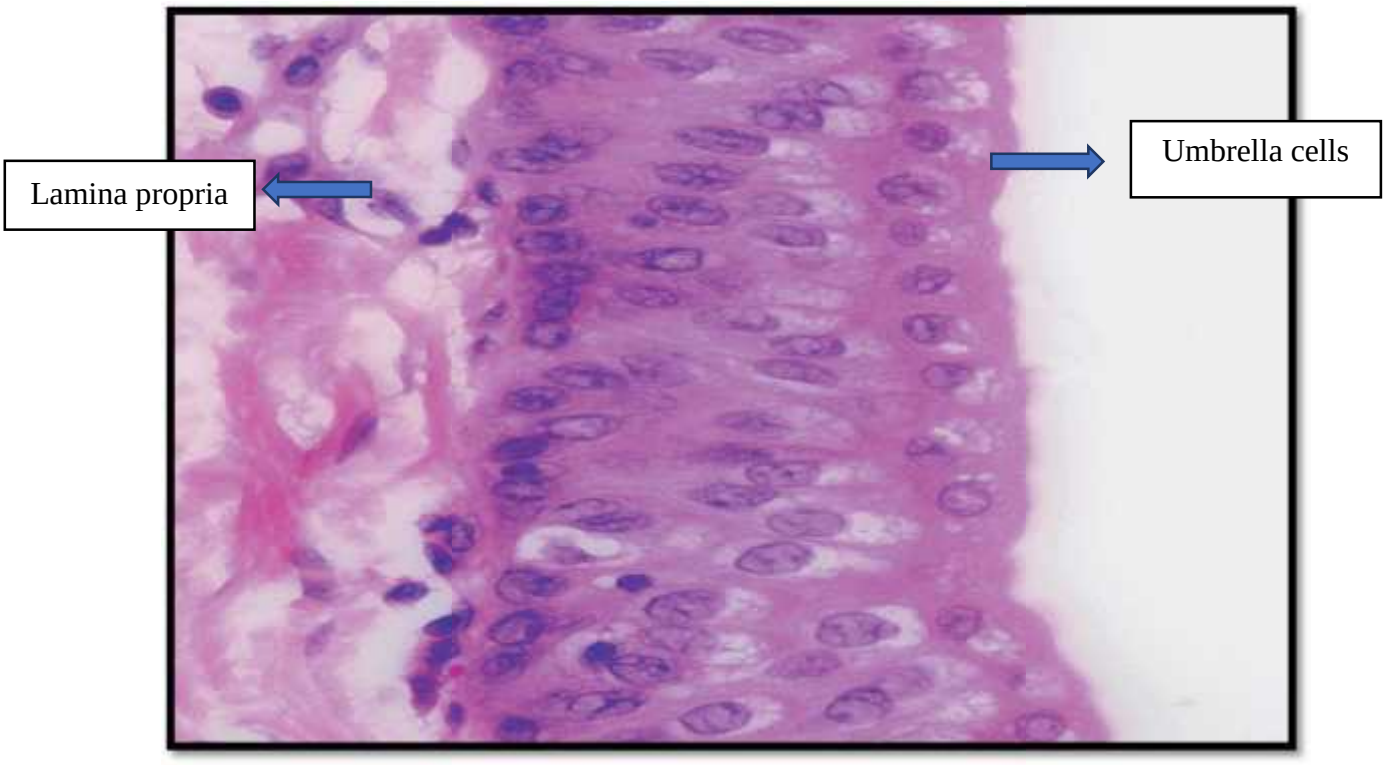


Fig3.3: Transitional epithelium with lamina propria, H&E, higher magnification[6]

Beneath the basement membrane is the lamina propria made up of abundant connective tissue with few elastic fibers. It also has rich vascular network, sensory nerve endings and lymphatic channels along with small fascicles of smooth muscle bundles in its upper part forming muscularis mucosae. This has to be carefully differentiated with the underlying muscularis propria, which is important in assessing tumor staging and subsequent treatment.[11]

The muscularis propria, also called as detrusor muscle is made up of loosely arranged smooth muscle bundles in three layers. The inner and outer layer being longitudinal muscles and middle is the circular muscle bundles.[6]The outer most layer of bladder is the adventitia, wherein only the superior surface is covered by serosa of the peritoneum. [11]

Metaplastic lesions(Variants of normal histology)

As already mentioned, the inner surface of the bladder which is lined by urothelium, changes its morphology depending on the state of bladder.During this process(exposure to injurious stimulus or inflammatory insult) it transforms into benign morphological traits, which forms the variants of normal histology. The most common among such is the formation of Von Brunn nests from the urothelium.[11]

Von Brunn nests

Von Brunn nests are formed by the invagination of the urothelial cells into underlying lamina propria. Over a period of time they lose connection from the overlying epithelium and presents in the superficial lamina propria. [11]

Cystitis cystica and cystitis glandularis

The term cystitis cystica has been named when these Brunn nests in the lamina propria is showing cystic dilatation along with central lumina formation. Whereas in cystitis glandularis the lining epithelium undergoes glandular metaplasia.The superficial umbrella cells in the above conditions becomes cuboidal to columnar and the luminal spaces show homogenous eosinophilic material. If these lining cells show morphology similar to goblet cells then it is coined as cystitis glandularis with intestinal metaplasia. In cases of inflammatory insult, the lining urothelium can even undergo squamous metaplasia.[11]

INFECTIONS AND INFLAMMATION

Cystitis

Cystitis is the most common inflammatory condition of urinary bladderand can presents as acute and chronic forms. It is further classified into various types depending upon the cause, duration and histological appearance. It can be caused by

many bacteria, viruses, fungi and protozoa, but most common being bacterial infection from Escherichiacoli organism.[1,4]It can also be seen secondary to bladder calculi, any local trauma, chemotherapy or radiation therapy.[11]

Polypoidal cystitis

These refers to broad based edematous lesions which are often associated in patients with long term indwelling catheters. Microscopically the papillary fronds are broader than papillary carcinoma, urothelium demonstrates mild hyperplasia. Underlying lamina propria shows edematous stroma with dilated blood vessels and chronic inflammatory infiltrate.[9,13]

Follicular cystitis

It is seen in 35% of patients with urinary tract infections and 40% of patient with having bladder cancer. On cystoscopy, it is appreciated as pale pink to grey nodules in a background of erythematous mucosa. On microscopy these nodules are composed of lymphoid follicles having prominent germinal center which are distributed in the lamina propria.[9]

Hemorrhagic cystitis

This group of cystitis is caused by chemical toxins like cyclophosphamide, alkylating agents, busulfan, viral infections, derivatives of aniline and toluidine (dyes and insecticides exposure).[9,11]

Microscopically, mucosa shows extensive areas of ulceration and thinning along with purulent exudate. Underlying lamina propria shows large areas of hemorrhage and edema. In the recovery phase, epithelium turns to be hyperplastic with increased mitotic activity and lamina propria shows many macrophages and fibroblasts.[11,14]

Eosinophilic cystitis

It is a uncommon clinic-pathological condition of the bladder which typically show transmural inflammatory infiltrate comprised of eosinophils often associated with fibrosis with or without muscle necrosis.[15]The lesions was first explained independently by Brown and Palubinkas in 1960.[16]The cause is uncertain though it is usually associated with conditions like allergy, bladder trauma, tumors, parasitic infection, chemotherapeutic agents. The initial trigger is due to formation of immunoglobulins as a result of antigen-antibody reaction. These in turn activates eosinophils leading to inflammatory process.[15]Both medical and surgical management is recommended such as transurethral resection of the bladder lesion along with nonsteroidal anti-inflammatory agents and antihistamines followed by Steroids, Cyclosporin-A and azathioprine as second and third line agents.[15,16]

Infectious cystitis

Bacterial cystitis is the most common in this group and arecaused by coliform organisms like Escherichia coli, Klebsiella pnuemoniae and Streptococcus faecalis. Other less common etiological agents includes Proteus vulgaris, Pseudomonas pyocyanea, Neisseria gonorrhea, Salmonella typhi and Diphtheroids.[9]

*Tuberculous cystitis*which is usually secondary to renal tuberculosis is caused by Mycobacterium tuberculosis. Early lesions are localized near ureteric orifice having remarkable congestion and edema. Later these lesions enlarge in size forming tubercles. Tubercles then coalesce and ulcerate forming fibrino necrotic exudate. On microscopy, many caseating granulomas along with Langhan type of giant cells are seen localized to lamina propria with areas of mucosal ulceration.[9,11]

*Schistosomal cystitis*is more prevalent in Nile valley and Sub Saharan Africa. It is caused by trematode Schistosoma hematobium which resides in para vesical

venous plexus.From the para vesical plexus the ova gets implanted into the veins of muscularis propria. As they degenerate it elicit a granulomatous response comprised of perioval fibrosis surrounded by lymphocytes, macrophages and giant cells. The chronic Schistosomal cystitis has the high incidence of progressing towards carcinoma of bladder especially squamous cell carcinoma.[9,11]The incidence of squamous cell carcinoma is very low constituting around 1.3% of all bladder tumors in males and 3.4% in females.[4]

Fungal and Actinomycotic cystitis forms the next group in infectious cystitis. Fungal cystitis is often rare, caused by Candida albicans and occasionally by Aspergillus. It is acquired as ascending infection from urethra or from hematogenous route. Classical hyphae and yeast forms are demonstrated on routine H&E sections, Periodic acid schiff or methenamine silver stains.Actinomycotic cystitis is usually rare and seen secondary to infection of ovary and fallopian tube. The lesions may show mucosal edema and erosion, full thickness involvement of the bladder wall, which may result in fistula formation.[9]

Malakoplakia

It is an unusual form of granulomatous response that occurs as a result of defective phagocytosis of bacteria by mononuclear cells. The condition was first explained by Michaelis and Gutmann in 1902. It was derived from Greek word, where *Malakos* means soft and *Plakos* means plaque. Thus grossly they are appreciated as multiple, soft, yellow plaques with central umbilication and peripheral rim of congestion. Microscopically, mucosa is intact, lamina propria shows dense histiocytic infiltrate having granular eosinophilic cytoplasm. The cytoplasm also contains concentric basophilic laminated inclusions with a bull's eye appearance called as Michaelis-Gutmann bodies.[9,11]

Special types of cystitis[9]

This includes,

Interstitial cystitis (Hunner ulcer)

BCG granuloma

Noninfectious granulomas- suture granuloma, granulomas of rheumatoid arthritis

Radiation cystitis

URINARY BLADDER NEOPLASMS

Urinary bladder tumors is the ninth most common tumor worldwide.[17]It constitutes the second most common tumor of the genitourinary tract next to prostate.[18] There is a steady increase in the incidence rate of these cancers over last 60-70 years.[10]Majority of the tumors are urothelial in origin.[1]Urothelial carcinoma is the most common type accounting to 90% of all primary tumors of urinary bladder.[4]Urothelial carcinomas are also seen at other sites such as renal pelvis, ureters, urethra in the decreasing order of frequency only next to urinary bladder.[19]

Global scenario

According to global cancer statistics 2012 data, approximately 4.29 million new cases of bladder cancer and 1.65 million deaths due bladder cancer has been registered worldwide. It is more common in males constituting 75% of the total burden of the disease.[17]

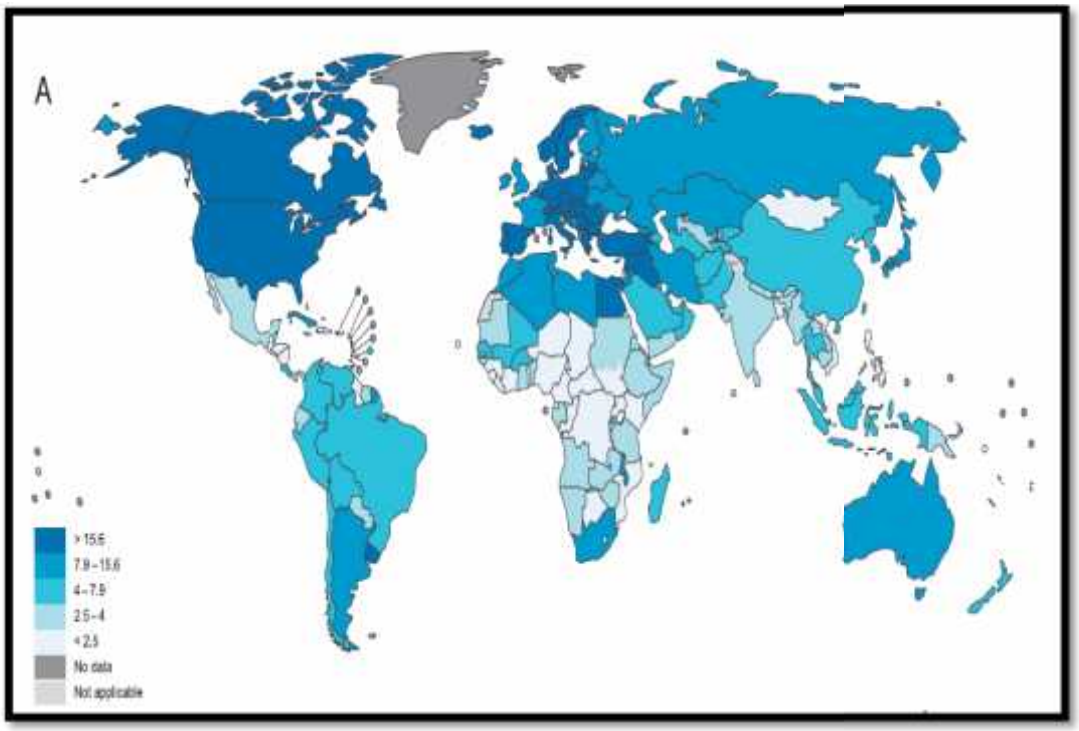


Fig 3.4: Age-standardized incidence rates for Men among various countries across world in 2012.[17]

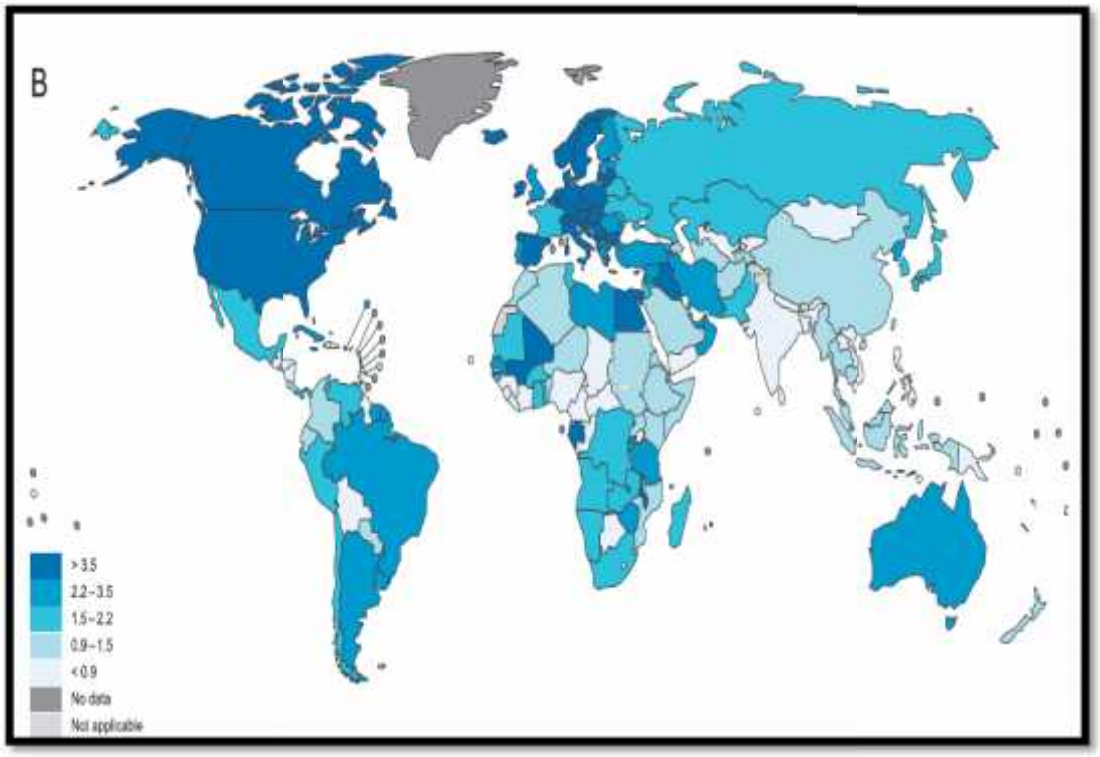


Fig 3.5: Age-standardized incidence rates for Women among various countries across world in 2012.[17]

Incidence rates are more in regions like Europe, North America, West Asia and Northern Africa while lowest in Eastern, Middle and Western Africa. The highest mortality rates are seen in Turkey (12.8 per million).[20]There is wide variation in global burden of bladder cancer noticed during the surveillance. Around 55% of all bladder cancer cases and 43% of all mortality due to bladder cancer are observed in 20% of global population residing in developed countries. On the other hand, only 5% of cancer burden is observed in people residing in underdeveloped countries.[17]

In areas like Africa and Western Asia the cancer burden is attributed to infection of Schistosoma hematobium which usually shows squamous cell carcinoma on histology. This contributes to 50% of the bladder cancer in Africa and 3% of cancer worldwide.[20]

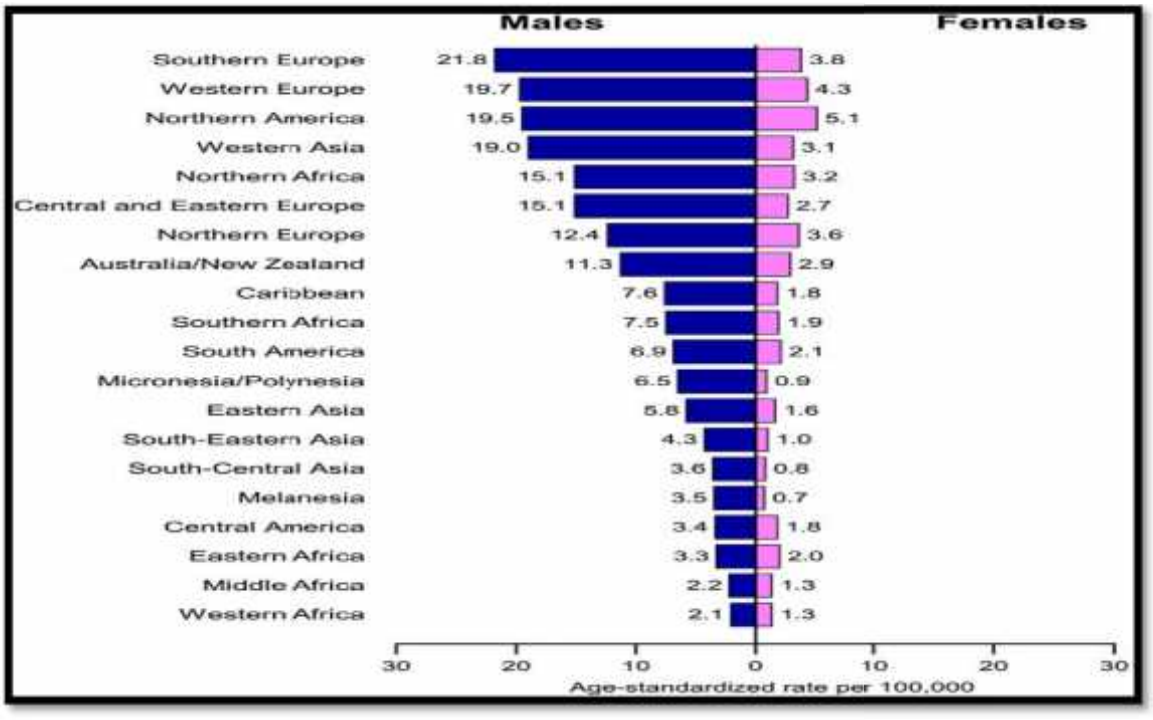


Fig3.6: Urinary Bladder cancer incidence rates according to world area and sex[20]

National scenario

According to National Cancer Registry Programme 2012-2014, the incidence of Urinary bladder cancer is high in metropolitan cities which is given as Age Adjusted Ratio(AAR, number of cases per 1 million population). The AAR is highest in Delhi (7.4) followed by Thiruvananthapuram (4.9)for males. Then comes the Mumbai(4.1), Kolkata(4.0), Chennai(3.0), Bhopal(2.7) and Bangalore(2.4) in the decreasing order of incidence.[21]

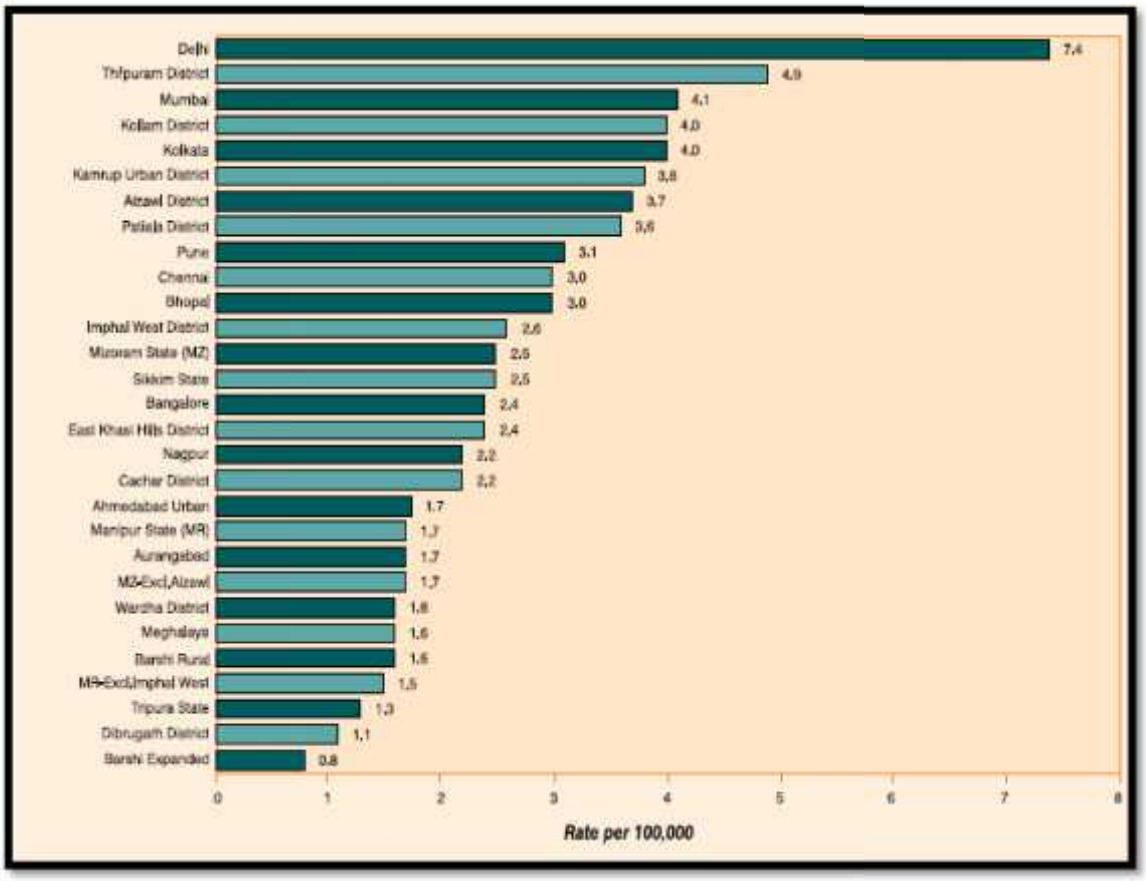


Fig3.7: Comparison of Age Adjusted Incidence Rates for Urinary Bladder cancer in various major cities of India[21]

According to Indian Cancer Registry data, it is the ninth most common cancer accounting to 3.9% of all cancers. Both benign and malignant lesions are well documented carrying significant morbidity and mortality. These malignancy

manifestwith complex and heterogenous signs and symptoms with a wide histopathological spectrumthus posing problem to urologists and pathologists.[4]

Urinary bladder tumors are more common in men than in women with a ratio of 3-5:1 and in urban than in rural people. The prevalence of bladder tumors is six times more common in developed countries than in developing countries.[19,22]Around 80% of the people fall in the age group of 50 - 80 years.[1]

Despite the implementation of new surgical techniques, intravesical and systemic treatments, 30% of noninvasive urothelial carcinoma and 50% of the invasive urothelial carcinoma manifests with disease progression followed by recurrence and eventually death.[4]

Etiology and Pathogenesis

Bladder cancer, with rare exceptions, is not familial.[1]The association between some of the etiological agent in evolution of bladder cancer is well established. They can be either genetic abnormality or external risk factors like cigarette smoking, occupational carcinogens from chemical industry, Schistosoma hematobium infection in endemic areas, use of artificial sweeteners, patients on long term use of cyclophosphamide and analgesics and patients receiving radiation therapy for uterine cancers.[1,23,24]

Genetic factors such as null GSTM-1(Glutathione-S transferase) and slow NAT-2(N- acetyltransferase) polymorphism increases the risk of bladder cancer. These conjugates with several reactive compounds like aryl amines and nitrosamines and detoxifies them, which are known bladder carcinogens. The first degree relatives are at increased risk of developing urothelial cancers by two times than the normal population.[10]

Urinary bladder constitutes the main internal organ affected by occupational carcinogens apart from lungs and skin. Occupational exposure to aromatic amines such as naphthylamines, benzidine and biphenyls relatively increases the incidence of bladder cancer. These organic amines are used in chemical, rubber, paint, dyestuff and textile factories and also in laboratory works, leather work and printing units.[10,11]

Cigarette smoking specifically has two to six times increased chance of developing bladder cancer, which is directly related to intensity and duration of smoking.[10]

Many nutritional agents like salted and barbequed meat, pork, Soy and spices along with artificial sweetners like Saccharine or cyclamates are linked to have increased risk of development of bladder cancers.[10]

Analgesic abuse such as high dose of Acetaminophen or Phenacetin, long term use of cyclophosphamide have been related to increased risk of both bladder and renal cancers. Radiation exposure as a part of therapeutics in patients with prostate or cervical cancer and also atomic bomb radiation increases the relative risk of bladder cancer by 1.63 in men and 1.74 in women. [10]

Among parasite, Schistosoma hematobium is a known risk factor in development of Squamous cell carcinoma. The other infectious agents like Human papilloma virus via its proteins E6 and E7 have found to act upon TP53 tumor suppressor gene in progression towards malignancy. Chronic bacterial infections caused by Escherichia Coli and Pseudomonas have found to increase the risk of developing Bladder cancer by 1.4 to 1.6 times. [10]

Many tumor suppressor genes and oncogenes role has been established in invasive urothelial carcinoma. These include mutations of TP53, FGFR3, PIK3CA, RB1 and HRAS with TP53 and FGFR3 together with promoter mutations of TERT.[25]

Two models are hypothesized in explaining the bladder carcinogenesis. First model explains the cancer initiation by deletion of tumor suppressor gene on 9p and 9q. This leads to formation of superficial papillary tumors, which may acquire subsequent mutations in TP53 gene progress to invasive carcinoma. The second model explains the development of carcinoma in situ in the beginning by TP53 mutations. This will progress to invasive carcinoma with loss of chromosome 9.[1]

These superficial tumors further undergo genetic alteration by mutations in fibroblast growth factor receptor 3 (FGFR3). This leads to activation of RAS pathway. While in the invasive tumors there is loss of function mutation in the TP53 and RB gene (retinoblastoma tumor suppressor gene).[1]

Mutations involvingTP53, RB, PTEN pathways are most commonly associated with invasive carcinoma and the combined mutations of all the three pathwaysfollows a much worse prognosis. [10]

Clinical features

- Gross and microscopic hematuria constitutes the main symptoms in many of the bladder neoplasms.[26]
- Painless hematuria is the most common complaint often seen in 85% of patients with bladder cancers. This is followed by clotting resulting in painful micturition.[26]
- The large tumors will reduce the capacity of bladder thereby leading to increased frequency.[26]
- Apart from this, tumor near the bladder neck, having carcinoma in situ or spreading over a large area may lead to complaints like dysuria, urgency, increased frequency and acute retention of urine.[1,18,26]
- Tumors obstructing the ureteral orifice lead to hydronephrosis.[26]

- Patients with advanced disease may present with palpable suprapubic mass or edema of lower limbs. In cases of metastasis, weight loss with abdominal or bone pain is often noticed.[26]

The chances of recurrence depend on various factors such as tumor size, stage, grade, multifocality, number of mitotic figures and associated features such as dysplasia with or without carcinoma in situ in the adjacent mucosa.[1]

Most of the recurrence arises from shedding of these tumor cells from its primary site. These shed tumor cells implant on other site causing recurrence. This explains the fact that why the recurrent tumors express the same clonality though it arises at the site other than the primary.[1]

MORPHOLOGY OF VARIOUS UROTHELIAL AND NON-UROTHELIAL NEOPLASMS- THE 2016 WHO CLASSIFICATION OF TUMOURS OF URINARY SYSTEM(4TH EDITION)

***Table3.1*: Classification ofNon-invasive Urothelial Neoplasm**[25]

Urothelial carcinoma in situ [CIS]
Papillary Urothelial Carcinoma, Low grade [NIPUC- LG]
Papillary Urothelial Carcinoma, High grade [NIPUC- HG]
Papillary Urothelial Carcinoma of low malignant potential [PUNLMP]
Urothelial papilloma
Inverted Urothelial Papilloma
Urothelial proliferation of uncertain malignant potential
Urothelial dysplasia

Urothelial proliferation of uncertain malignant potential

This entity has been newly added in fourth edition (2016) of WHO classification of tumors of urothelial tract replacing the old term papillary urothelial

hyperplasia. These lesions are seen as de novo, patients with prior history of carcinoma or seen as a shoulder lesions in areas adjacent to papillary neoplasms. It is characterized by thickening in the lining urothelium with minimal or no cytologic atypia. There are no true papillary fronds although undulations can be seen rarely.[25]

Urothelial dysplasia

These are believed to be pre-neoplastic condition that show characteristic flat lesions with reasonable architectural and cytological atypia. But they does not fulfill the criteria of urothelial carcinoma in situ.[25] These are histologically characterized by architectural abnormality and nuclear atypia but will fall short for fulfilling criteria of carcinoma in situ. The cells show nucleomegaly with irregular nuclear membrane and hyperchromasia.[27]

Urothelial papilloma

These are relatively rare benign condition accounting for <1% of all papillary urothelial lesions which is most commonly seen in young patients presenting as small, discrete, papillary growth. These papillae are lined by urothelium with normal thickness and cytology having prominence of superficial umbrella cellsand fibrovascular core in the center.These papillae has to be differentiated from those of papillary carcinoma by their characteristic short and broad papillae. The recurrence after excision and progression to carcinoma is extremely rare event.[11,28]

Inverted urothelial papilloma

Inverted papilloma are rare benign lesions which are often confused with urothelial carcinoma. They are most commonly seen in urinary bladder. But can occur anywhere in the urinary tract other than bladder like renal pelvis, ureter or urethra in the decreasing order of frequency. The important clinical manifestation includes

hematuria and are seen as polypoidal mass which are either sessile or pedunculated on cystoscopy.[11]

On microscopy, there is anastomosing nests and cordsof overlying urothelial cellswhich are seen in lamina propria as endophytic growth. These nests are lined by benign looking urothelial cells which are arranged towards the center and periphery is lined by basal cells. They show orderly maturation and occasional mitoses which are placed towards the basal layer of urothelium.[4,11]

These inverted papilloma has to be differentiated from urothelial carcinoma having endophytic growth pattern. The presence of cytological atypia, irregularity in thickness of the lining urothelium and irregular sizes of nests within lamina propria and the desmoplastic reaction offers clue to distinguish them.[11]

Papillary urothelial neoplasm of low malignant potential **[PUNLMP]**

These are the papillary urothelial neoplasms which resembles urothelial papilloma but show mild increase in thickness of the lining epithelium. They often show delicate papillae which are lined by neoplastic urothelial cells having mild architectural abnormality and minimal cytological atypia. The individual cells maintain the polarity with respect to basement membrane. They show relative similarity with each other with respect to size, shape and color. Mitosis though rare are limited to basal layer. However, 7-10% of them progress to urothelial carcinoma during the recurrence.[11]

Table 3.2: Histologic features proposed by WHO/ISUP (2004) to classify various papillary urothelial lesions[2]

	Papilloma	***Papillary urothelial neoplasm of low malignant potential***	***Noninvsive papillary urothelial carcinoma, low grade***	***Noninvsive papillary urothelial carcinoma, high grade***
Architecture				
Papillae	Delicate	Delicate, occasionally fused	Fused, branching, and delicate	Fused, branching and delicate
Organization of cells	Identical to normal	Polarity identical to normal; any thickness, cohesive	Predominantly ordered, yet minimal crowding and minimal loss of polarity, any thickness, cohesive	Predominantly disordered with frequent loss of polarity; any thickness, often discohesive
Cytology				
Nuclear size	Identical to normal	May be uniformly enlarged	Enlarged with variation in size	Enlarged with variation in size
Nuclear shape	Identical to normal	Elongated, round-oval, uniform	Round-oval, slight variation in shape and contour	Moderate - marked pleomorphism
Nuclear chromatin	Fine	Fine	Mild variation within and between cells	Moderate-marked variation both within and between cells with hyperchromasia
Nucleoli	Absent	Absent to inconspicuous	Usually inconspicuous	Multiple prominent nucleoli may be present
Mitoses	Absent	Rare, basal	Occasional, at any level	Usually frequent, at any level
Umbrella cells	Uniformly present	Present	May be absent	Absent

Urothelial Carcinoma in situ **[CIS]**

It is characterized by evidence of cytologically malignant cells in the urothelium layer without breach in the basement membrane.[1]The cells are haphazardly oriented with nuclear crowding and overlapping. Nucleus of these cells may show pleomorphism, hyperchromasia with variable nucleoli. [27]These lesions tend to be multifocal, often involves entire bladder surface and extends to ureters and urethra. The cells are dyscohesive and are shed in urine, which can be detected on urine cytology. Unless treated, 50-75% of the CIS lesions progress to become muscle invasive tumors.[1]

Invasive urothelial carcinoma **[IUC]**

As in 2004, the new 2016 classification continues to recommend the use of 1997 ISUP system for grading of the tumors.They have remarkable propensity for divergent differentiation. The incidence of invasive carcinoma with divergent differentiation forms 33% in radical specimens. However, data is limited to establish the outcome of patients depending on the degree of divergent differentiation.[25]

Evaluation of Primary tumor in urinary bladder includes a multistep approach, like radiological studies, Cystoscopic examination and histopathological study for confirmation of tumor. During Cystoscopy, one should evaluate for location, size, number and appearance of growth. Further presence of bladder wall thickening with a mobile mass indicates T3 and fixed mass indicates T4 disease.[29]

The sampling of muscularis propria is very important to confirm its involvement by tumor or not. Repeat biopsies from the early invasive tumors(T1) will help to provide appropriate staging and assessment of tumor progression.[29]

Regional lymph node sampling and staging has a significant role in prognostication. It is demonstrated that the outcome is good with metastatic disease to lymph node than the metastasis to other viscera and bone.[29]

***Table3.3**: **Classification of Invasive urothelial carcinoma*[25]**

Infiltrating urothelial carcinoma with divergent differentiation
Nested, including large nested
Microcystic
Micropapillary
Lymphoepithelioma-like
Plasmacytoid/signet ring cell/diffuse
Sarcomatoid
Poorly differentiated
Giant cell
Clear cell
Lipid rich

The IUC can be unifocal or multifocal lesions with wide range of gross morphology. They can present as papillary, nodular, polypoidal, solid, ulcerative or diffuse transmural growth. The adjacent mucosa can be either normal or hyperemic representing the areas of carcinoma in situ on microscopy.[26]

Microscopically,majority of pT1 carcinomas demonstrate papillary pattern and are low or high grade. Whereas pT2-T4 carcinomas are non-papillary and high grade. The grading of these carcinomas into low and high grades are done based on the nuclear anaplasia and architectural abnormality.[26]

The most important aspect during microscopic evaluation of these urothelial carcinomas is identification of invasion and commenting on the extent of invasion. This is characterized by presence of nests, clusters or singly scattered tumor cells in the lamina propria or muscularis propria. The evidence of invasion is further supported by presence of desmoplastic response and tumor cells within retraction spaces.[26]

Generally, the tumor cells present as infiltrating cohesive nests with occasional palisading along the edges of the nests. The nuclei are hyperchromatic, showpleomorphism with irregular nuclear membrane. Nucleoli will be small or large eosinophilic which may vary in number. Cytoplasm is moderate to abundant and is amphophilic in nature. Bizzare and multinucleated tumor giant cell along with atypical mitotic figures are common. The intervening stroma shows mild to marked lymphoplasmacytic infiltrate. Retraction artefacts are often noted along the edges of the tumor nests.[26]

The identification of the particular morphological variants in the invasive urothelial carcinoma is of prime importance as,

- Some variants of it are associated with different clinical outcome.
- Therapeutic approach differs depending on the histologic variant.
- Knowledge about the rare variants with unusual patterns is important in avoiding diagnostic misinterpretations.[30]

For defining IUC with divergent differentiation, the tumor should be arising from urothelium of the urinary tract containing the usual morphology of the urothelial carcinoma along with some percentage of other morphologic entities like squamoid, glandular, small cell and trophoblastic differentiation. The common morphological differentiation is seen to be squamous type which is identified in 40% of IUC.

Glandular differentiation is seen in up to 18% of IUC followed by other rare types like small cell and trophoblastic differentiation.[25]

Squamous differentiationis the most common variant of urothelial carcinoma which is identified in around 16.8 to 40% of cases with male predominance.[31,32]It is identified by looking at the clear-cut evidence of malignant squamous cells having intercellular bridges and forming intracellular keratin along with keratin pearls showing variable degree of squamous differentiation, sometimes to an extent that it is associated with urothelial carcinoma in situ as the only urothelial component.[30,31]It often demonstrates high rates of advanced tumor stage with lymph node metastasis and poor prognosis but evidence is still not established it to be an independent prognostic factor.[31]

Glandulardifferentiation is identified by formation of gland-like spaces along with small tubules.[30]The glands may be variable in appearance. Tubules may be small, tubular and evenly spaced or moderate to large sized, closely packed and irregular.[28]

Nested variantis the rare and aggressive form composed of cytologically bland tumor cells. They present as discrete or cohesive small nests or tubules within the lamina propria giving an appearance of urothelial proliferations such as Brunn nests and cystitis cystica. Thus, differentiation can be made by looking at the tumor cells showing anaplasia, coarse chromatin, large nucleoli and evidence of irregular and infiltrative border at the deeper levels.[25,26]

Micropapillary varianthas been well documented and distinct entity. It is characterized by multiple small nests without fibrovascular core comprised of markedly anaplastic tumor cells. The distorted nuclei and cytoplasmic vacuoles are commonly seen. This particular variant of urothelial carcinoma is always a high

grade, presents with a high pathological stage and high incidence of metastasis with poor outcome. Genetically, there is overexpression and amplification of HER2 in this particular variant than conventional urothelial carcinoma[25,26]

Plasmacytoid variant is characterized by presence of single, discrete mononuclear tumor cells showing plasmacytoid, lymphoid or rhabdoid features in loose stroma. The tumor cells demonstrate variable amount of intracellular mucin deposition imparting signet ring cell appearance. But there is no evidence of extracellular mucin. At molecular level, they demonstrate somatic loss of function mutations of CDH1 gene and loss of e-cadherin expression.[25]

Sarcomatoid variantis usually associated with previous history of bladder carcinoma either treated by radiation or cyclophosphamide therapy. Grossly, they are "sarcoma-like" with dull gray, polypoidal or intravesicular masses having infiltrative borders. Microscopically, they are composed of epithelial component comprised of urothelial, glandular, small cell elements with variable degree of differentiation. The mesenchymal component shows heterologous elements such as osteosarcoma, chondrosarcoma, rhabdomyosarcoma, leiomyosarcoma and liposarcoma.[26]

Clear cell variantof IUC is a very rare tumor containing abundant PAS positive glycogen material and is negative for mucicarmine and oil red O. The tumor shows sheets and nodules lined by malignant cells which are round to polygonal having nuclear atypia, prominent nucleoli and abundant clear cytoplasm without any hob nailing and lumina formation. Immunohistochemically these cells are positive for CK7, p53, p63, vimentin, E-cadherin (focal positivity) and negative for CA125, CD117, CK20, PAX 8, PLAP, PSA, Uroplakin III. The main differential diagnosis to be considered are clear cell adenocarcinoma which usually show hob-nailing and are positive for mucicarmine and PAX 8. The lipid- rich variant of urothelial carcinoma

contains large pleomorphic cells with multiples cytoplasmic vacuoles mimicking lipoblast-like appearance. Metastatic disease with clear cell morphology to be considered are renal cell carcinoma (negative for CK7 and CK20 and positive for CAM5.2, PAX 8), clear cell carcinoma of prostate, lung, breast, uterus, ovary and vagina should also be differentiated.[33,34]

The undifferentiated variant of IUC of 2004 classification has been renamed as "poorly differentiated" variant in 2016 classification and includes those tumor containing osteoclast like giant cells also.[29,34]

Table 3.4**: **New entities added among Non-urothelial neoplasms in 4th edition[25]

-Urachal carcinoma	***- Mesenchymal tumors***
-Tumors of Mullerian- type	Inflammatory Myofibroblastic tumor
Clear cell carcinoma	Perivascular epitheloid cell tumor
Endometrioid carcinoma	Solitary fibrous tumor
-Neuroendocrine tumors	Granular cell tumor
Small cell neuroendocrine carcinoma	***-Miscellaneous tumors***
Large cell neuroendocrine carcinoma	Tumors of upper urinary tract
Well differentiated neuroendocrine carcinoma	Tumors arising in a diverticulum
Paraganglioma	Urothelial tumors of urethra

Squamous cell neoplasms

Squamous cell neoplasms are derived from urothelium showing histologically pure squamous cell phenotype.[35]It constitutes 3 to 6% of bladder cancers in Schistosoma non-endemic areas and up to 75% of Schistosoma endemic areas. The male to female ratio is lower for these squamous cell neoplasms.[28]The main etiological factors associated with it are tobacco smoking, schistosomiasis and chronic

irritation and inflammation. Its diagnosis is restricted to pure squamous cell carcinomas.[35]The recent WHO classification has remained same for these group of neoplasms andincludes pure squamous cell carcinoma, verrucous carcinoma and squamous cell papilloma.[25]

Glandular neoplasms

Glandular neoplasms are derived from urothelium showing histologically pure glandular phenotype.[36]It accounts for 0.5 to 2% of all bladder cancers having male to female ratio similar to that of urothelial carcinomas. Microscopically it usually show glandular or papillary growth pattern but may also show solid areas in cases of poorly differentiated tumors. These glandular spaces resemble typical intestinal adenocarcinoma. These lesions has to be differentiated from urothelial carcinomas with glandular differentiation by demonstration of retained expression of high molecular weight cytokeratin and p63 in the latter. Whereas, adenocarcinoma fail to express these markers and are positive for CDX-2.[28] The 2016 WHO classification has removed signet ring cell and clear cell variants of adenocarcinoma from these glandular neoplasms group and added them in IUC.[25]

Urachal carcinomas

Urachal carcinoma is one of the rare non-urothelial tumor which are often seen in ovaries but less frequently in adnexa and urinary bladder. It constitutes about 0.01% of all malignant lesions and 0.1-0.3% of all urinary bladder tumors. They arise from the urachus, which presents as a fibromuscular band connecting umbilicus to apex of bladder and it is called median umbilical ligament. Hence they usually invades bladder at its apex or anywhere along the midline. Thus it becomes difficult for its early detection. They are most commonly seen in men in their 5^{th} decade of life and carries poor prognosis as there is no effective treatment presently.[37]

It is classified into 5 histologic subtypes namely: Intestinal, Mucinous, signet ring, Unspecified and Mixed type by Grignon *et al* in 1991. It is usually diagnosed and staged on the basis of two theories put forth by Sheldon et al in 1984 and Mayo staging system in 2006. The most common sites of the metastasis in urachal carcinomas are lymph nodes, peritoneum and lungs.[37]

Tumors of Mullerian origin

This subcategory was added in 2016 WHO classification and includes clear cell carcinoma and endometrioid carcinoma.[25] This clear cell carcinoma of urinary bladder is more common in women than men and arises due to malignant transformation of endometriosis focus. Most common sites being urethra, trigone or posterior wall of bladder.They are histologically and immunohistochemically identical to clear cell carcinoma of female genital tract. They are positive for CA-125, PAX8, pancytokeratin and CK7. [38]

Neuroendocrine tumors

This includes small cell, large cell, well differentiated neuroendocrine carcinomas and paraganglioma and constituets <1% of all tumors. These are histologically similar to their pulmonary counterpart and are occasionally seen in bladder with male predominance. They often carry worse prognosis compared to urothelial carcinomas with small cell carcinoma having bad outcome. [39]

Melanocytic tumors

It includes malignant melanoma, naevus, melanosis.[25] Primary malignant melanoma is very rare with equal gender predilection. The diagnostic criteria includes - no evidence of cutaneous melanoma, no skin or mucosal melanoma traced on careful examination, no evidence of itssubsequent development over these surface, pattern of

metastasis similar to bladder origin, evidence of intra mucosal melanocytes at the edge of the tumor.[28]

Mesenchymal tumors

This includes rare heterogenous group of lesions like benign and malignant mesenchymal tumors along with reactive pseudo sarcomatous lesions which are tumor like changes.[40]Leiomyoma is most frequently encountered, other benign lesions reported includes hemangioma, lymphangioma schwannoma, granular cell tumor, solitary fibrous tumor, inflammatory myofibroblastic tumor, benign fibrous histiocytoma. Malignant tumors often include all types of sarcomas most common being leiomyosarcoma and rhabdomyosarcoma.[28]

Urothelial tract hematopoietic and lymphoid tumors

Primary Non-Hodgkins lymphoma is very rare in bladder. The one which are most commonly reported are B-cell lesions of mucosa-associated lymphoid tissue type, diffuse large B-cell lymphoma and some T-cell lymphomas.Secondary involvement in a process of systemic lymphoma is noted in 10-20% of cases with Non-Hodgkins lymphoma.[28,41]Secondary involvement of bladder in leukemia patients is seen in 25% and 15% of cases of acute and chronic leukemia respectively. Both multiple myeloma and plasmacytoma rarely arise in bladder and are common in adults. [28]

Pathological Staging of bladder carcinoma

Jewett and Strong in 1946, first put forward the usefulness of assessing the depth of invasion as one of the important prognostic factor in bladder cancer and proposed the staging system. The above system was later modified and adopted by American Joint committee of cancer (AJCC) and is used worldwide now.[11]

The pathological staging of the invasive tumors helps in prognostication of the patients. It depends on both gross and microscopic examination of partial and radical cystectomy specimens. [29]

Gross examination is important in evaluating the extravesical spread and subcategorizing the pT3 stage. It also helps in identifying the independent primary tumors of prostatic urethra, to assess direct spread to prostate and seminal vesicles.Microscopic examination helps to rule out presence or absence of noninvasive or invasive carcinoma, depth of invasion, evaluation of surgical margins for involvement by tumor. [29]

Fig3.8: Various levels of extension indicating tumor stage in primary bladder tumor [42]

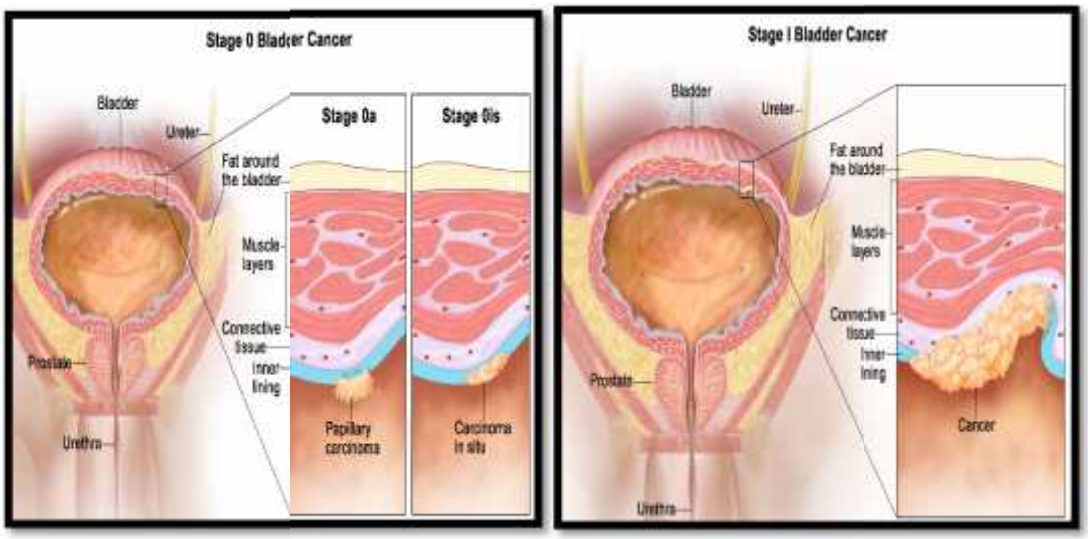


Fig3.8 A: showing **Stage 0a** (Non-invasive papillary carcinoma) and **Stage 0is**(urothelial carcinoma in situ: "flat tumors")

Fig 3.8 B: showing **StageI** bladder cancer (tumor invading into lamina propria: sub epithelial connective tissue) – refered as superficially invasive cancers [11]

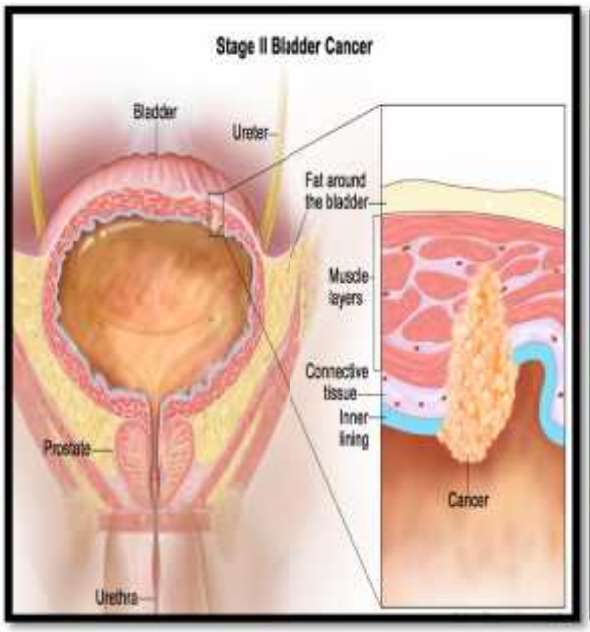


Fig3.8 C: showing **Stage II** of bladder cancer(tumor invading muscularis propria) which is further divided into **pT2a**(tumor invading superficial muscularis propria) and **pT2b**(tumor invading deep muscularis propria)

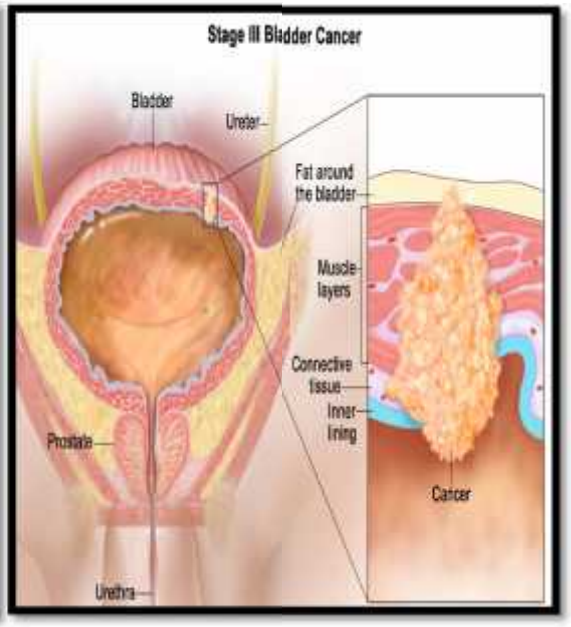


Fig 3.8 D: showing **Stage III** of bladder cancer (tumor invading peri vesical soft tissue) which is further divided into
pT3a(Microscopically) and
pT3b(Macroscopically: extravesical mass)

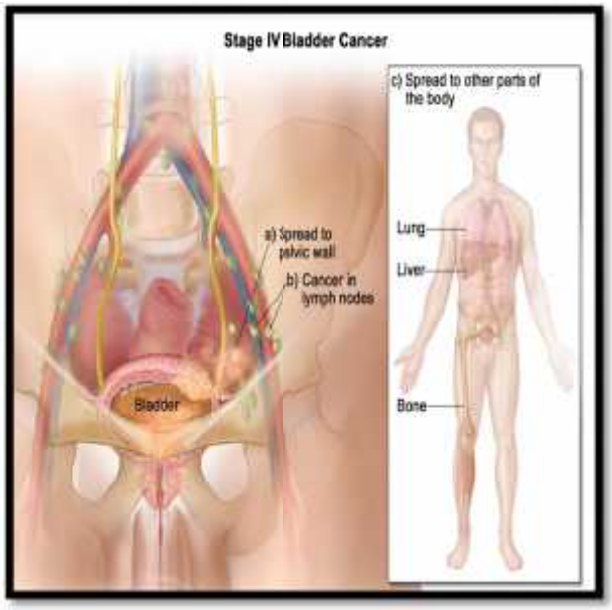


Fig 5.8 E: showing **Stage IV** of bladder cancer(extravesical tumor extension to any of the following like: prostatic stroma, seminal vesical, uterus, vagina, pelvic wall, abdominal wall) which is further divided into **pT4a**(invasion directly into prostatic stroma, uterus, vagina) and **pT4b**(invasion of pelvic wall, abdominal wall)

The risk of recurrence and disease progression does not solely depend on growth pattern and histologic grade of tumor. It also depends on various other factors such as,[25]

- Size
- Multifocality
- Time of recurrence
- Prior intravesical therapy

Much of the controversies regarding grading will be solved by use of ancillary techniques like Immunohistochemistry (IHC) or Molecular assay.[25]

Multiple IHC markers are extensively employedas potential predictors of tumor recurrence, progression or response to therapy.[43]These includes altered oncogenes, tumor suppressor genes, growth factors and its receptors, intermediate filament proteins and cell proliferation markers.[43]

p53, a nuclear phosphoprotein which plays a role of tumor suppression and modulates apoptosis, genetic stability and inhibits angiogenesis.Thus, any mutation in this gene results in accumulation of p53 in the nucleus of the cell which can be detectable with IHC. There is significant difference in expression of p53 among high and low grade of urothelial carcinomas with high grade carcinomas showing strong and diffuse positivity.[44]

The cell proliferation marker, Ki67 shows immunopositivity in the more than 50% of dysplastic cells lining the papillae in non-invasive high grade papillary urothelial carcinoma. This clearly decreases to less than 25% in cases of low grade carcinomas and even low among PUNLMP.[45]

p63, a nuclear marker of urothelium is helpful as diagnostic marker for high grade urothelial carcinomas for demonstrating microinvasions in to the lamina

propria. It also helps to distinguish carcinomas of urothelial origin from renal origin(negative).[45]

Cytokeratin 20, cytoskeleton associated with intermediate filament are predominantly expressed in superficial and intermediate layer of normal urothelium. Whereas its expression in the deeper layers of cells is seen in urothelial carcinomas. This property is used to differentiate urothelial papilloma from carcinoma.[44]

On the other hand, expression of CD44 (transmembrane polymorphic glycoprotein) is mainly localized to basal layers of urothelium. Loss of expression of CD44 and increased expression of CK20 is significantly associated with high tumor grade and stage.[43]

It is also significant to distinguish muscularis mucosa of lamina propria and muscularis propria in TURBT specimens. There can also be desmoplastic myofibroblastic proliferation mimicking smooth muscle bundles and are likely to be over diagnosed as muscularis propria. So they have to be differentiated with a panel of IHC markers such as vimentin, smooth muscle actin, desmin, caldesmon, smoothelin and CD10. Reactive myofibroblasts are positive for vimentin and smooth muscle actin and negative for the rest of markers. Whereas the non-vascular smooth muscle cells of bladder will express smooth muscle actin, desmin, caldesmon and negative for CD10. The smooth muscle bundles of muscularis propria show strong and diffuse positivity for smoothelin antibody. However, smooth muscle cells of muscularis mucosa including its hyperplastic variant may occasionally or in some cases showabsent, weak and focal or moderate immunoreactivity for smoothelin.[46,47]

CYSTOSCOPY

Cystoscopy is the endoscopic technique which is used to visualize the urethra and bladder mucosa and ureteral orifice. It is a quick, relatively painless minimally invasive procedureand can be done in the outpatient setting. It is the gold standard and primary diagnostic tool in cancer detection. It allows complete visualization of bladder mucosa followed by biopsy of suspicious areas for histopathological confirmation.[4,10]

The evolution of modern cystoscopes are the results of work by many pioneers. It has become a part of day to day practice in urology clinic. The present day performance of these instruments not only concentrates on the quality of patient care but also provides excellent image quality for educational purpose. Cystoscopy can also be used to access the upper urinary tract via ureters, called as retrograde ureteroscopy. This can be used either for diagnostic or therapeutic purpose.[48,49]

Theearliest efforts to develop Cystoscope was done by Philip Bozzini in 1805 which was the prototype of the current day cystoscopes.[48] The major advancement was done with the introduction of flexible fiber optics transmission system. In 1951, Harold Hopkins, a physicist applied fiber optics and patented the Hopkins lens system. The disadvantage with fiber optic system was its fragility and limited resolution of glass fibers. This led to the invent of distal chip sensor technology in 1970. This system converts light photons into a charge and then to an image. This offered a better durability, good resolution and a mode of storing the images in computers.[48] The advent of flexible fibre optic cystoscopy has dramatically changed the management of the urinary bladder tumors.[22]

Subtypes of Cystoscopy

Fluorescent Cystoscopy- this is used as an additional test during conventional cystoscopy which helps in diagnosis of bladder cancer. During the procedure, a porphyrin derivative (5-animolevulinic acid or hexaminolevulinate) is introduced. This gets accumulated on the cancer tissue and imparts a red glow in a blue fluorescent light.[48,49]

Fetal cystoscopy- here the flexible cystoscope is introduced into fetal bladder to identify the conditions causing obstruction (posterior urethral valve) or treat the condition like vesicoaminotic shunt. These helps in overcoming of lung and kidney maldevelopment.[49]

CT Virtual cystoscopy-it is a noninvasive technique and often doesnot requires anesthesia.Thus it is used in patients who are not fit for conventional cystoscopy.[49]

Narrow band imaging(NBI) cystoscopy- It has been introduced as an alternative endoscopic technique. It has increased the diagnostic accuracy among early malignant lesions of bladder. It uses red, green and blue filter bands of light spectrum for illumination of the target. Thus increasing the differentiation between mucosal surface and the underlying vascular network .[50]

Real time confocal laser endomicroscopy (CLE)- This technique has been introduced to upgrade the bladder cancer detection rates and its management. On CLE, benign and inflammatory lesions present as small and infiltrative areas with monomorphic loosely arranged cells in lamina propria without fibrovascular stalk.[51]

Low grade tumours appear as closely packed papillary structures with fibrovascular stalk. These papillae are lined by well organised high density monomorphic cells with absence of umbrella cells.[51]

High grade tumours also presents as papillary structures with fibrovascular core with distorted vasculature. But the cells ae disorganised, dyscohesive, pleomorphic with indistinct cells borders. [51]

CIS appears as heterogenous morphological entity containing pleomorphic cells with indistinct cell borders, inflammatory infiltrate and disorganised microarchitecture. [51]

Optical coherence tomography (OCT) - It is a non-invasive technique which is homologous to ultrasonography except that it uses infrared light instead of sound. It provides high resolution cross-sectional images by measuring back-reflected light. It has improved sensitivity and specificity in diagnosing superficial bladder tumours. [52]

Conventional cystoscopes can be of two types- Rigid and Flexible, having their own specific merits and demerits. Flexible cystoscopes are increasingly used in male patients whereas Rigid cystoscopes are mainly used in females for several reasons and benefits.[49]

Table 3.5: Rigid cystoscopes- advantages and disadvantages **[49]**

ADVANTAGES	DISADVANTAGES
Great variety of optics	Lithotomy position may cause discomfort
Better optics, lenses can be changed	Usually requires general anesthesia
Increased durability	Usually have large calibers
Simple structure and easy sterilization	Requires admission in hospital with overnight stay
Easy learning curve, only one hand required to work	More postoperative symptoms

***Table 3.6*:*Flexible cystoscopes- advantages and disadvantages*[49]**

ADVANTAGES	DISADVANTAGES
Usually done under short anesthesia	Small irrigating port
Less painful	Cannot change lens, complex sterilization
More patient position options	Irrigation and aspiration not possible without removing scope
Small calibers are available	Complex structure- chances of malfunctioning
Less possibility of overnight stay in hospital	Optics are suboptimal
Less postoperative symptoms	More learning curve, requires both hands

Complications

In majority of cases, postoperative period will be uneventful. Rarely, within first 24 hours after procedure patient may experience dysuria, increase in frequency or change in color of urine due to bleeding if cystoscopy is followed by biopsy. Patient may sometimes encounter episodes of mild to moderate fever, urinary tract infections. This will usually resolve spontaneously or may need short course of antibiotics. Another rare and serious complication include perforation of bladder. This requires emergency surgical repair of the bladder.[49]

TRANSURETHRAL RESECTION OF BLADDER TUMOR (TURBT)

TURBT is the most commonly practiced therapeutic and diagnostic procedure by urologists. The target of the procedure includes,[53]

- To establish the diagnosis of the tumor
- To identify the pathological staging of the tumor microscopically
- To ensure complete removal of Non-invasive papillary tumors of bladder

- To identify various clinical prognostic factors intra-operatively such as number, size, configuration, grade and presence of carcinoma in situ.

It is a multistep approach and should be performed in a systematic way to obtain an optimal results. After good anesthesia, urethra should be adequately dilated using an optical dilator to avoid trauma and bleeding. Once the 26F or 28F resectoscope is introduced the urine is collected for cytological examination. During the entire procedure the volume of the bladder should be maintained upto 50-70% of its capacity by instillation of fluid. Overdistension has to be avoided which results in flattening of mucosa and makes it difficult to visualize areas of CIS.[54]

Later, a pancystoscopy has to be performed to record the size, number, location and areas showing mucosal abnormalities.[53] A small papillary tumors ranging <1 cm can be removed en bloc with a part of underlying wall using a cold cup biopsy forceps or standard TURBT. While for a large tumors a differential resection has to be done using either monopolar or bipolar cautery.[53,54] The resected specimen has to be sent for pathological evaluation in separate container with labelling. This includes, resected part of the tumor, underlying bladder wall with detrusor muscle and edges of the resected areas. [53]

In addition to this, mucosal biopsies can be obtained from the other erythematous areas to evaluate presence of CIS. Complete hemostasis has to be obtained followed by insertion of catheter and bimanual examination.[53]

Assessing the quality of TURBT

- Although TURBT is practiced since decades without much changes, there is no clear quidelines for assessing its quality. But there are few general aspects accepted for successful procedure, such as [53]
- No residual Non-invasive lesion (decreased chances of early recurrence)[53]

- Correct staging of the lesion could be established with the sample provided (adequate sampling of the detrusor muscle)[53]
- Minimal post procedure complications.[53]

Complications of TURBT

Intraoperative complications include bleeding and bladder perforation which are encountered in 5-43% of cases. Other postoperative complications include infection, urinary retention and transurethral resection syndrome (TURS).[53] This TURS usually follow bladder perforation or silent extravesical absorption of the irrigating fluid. This can occur both during Transurethral resection of prostate(TURP) and transurethral resection of bladder tumors. Thus they are called “TURP syndrome” and “TURBT syndrome” respectively.[55]

It leads to water and electrolyte imbalance which takes usually 1-6 hours to manifest, which depends on the site of extravasation and the amount of extravasated fluid. The early manifestations include progressive distension of abdomen with discomfort, shoulder tip pain, nausea, chest pain along with symptoms of confusion and blurring. This later leads tohyponatremia, intravascular hypovolemia with an increase in total body water, hypotension, oliguria, acute renal failure, metabolic acidosis and altered sensorium.[55]

MATERIALS AND METHODS

This was a Prospective study was carried out in the histopathology laboratory of Department of Pathology in collaboration with Department of Urology, BLDEU's Shri B.M.Patil Medical College, Hospital and Research Centre, Vijayapura from 1st November 2015 to 30th June 2017.

It includes 48 cases of cystoscopic biopsies and TURBT specimens which were received in the histopathological department of Pathology

Inclusion criteria:

All the cystoscopic bladder biopsies and TURBT specimens which were received in department of pathology were included in the study group.

Methods of collection of data.

This is a prospective study of lesions of Urinary bladderand includes 48 specimens (Cystoscopic bladder biopsies and TURBT specimens) from patients received for histopathological examination, in the Department of Pathology, Shri B.M.Patil Medical CollegeHospital and Research Centre, Vijayapura during the period from 1st November 2015 to 30th June 2017.

The specimen were received in 10% formalin. The tissue was grossly examined first and findings were noted. The entire tissue was processed in all the cases.

The specimens were fixed in 10% formalin and processed as per standard procedure

Multiple sections of3-5 microns thickness were obtained from the paraffin block and stained with H & E.

Harris Hematoxylin and Eosin Stain (Regressive Stain)

Harris Hematoxylin

Hematoxylin Crystals	5.0 gm
Alcohol 10%	50.0 ml
Ammonium or potassium alum	100.0gm
Distilled water	1000.0ml
Mercuric oxide(red)	2.5gm

Dissolve hematoxylin in alcohol and alum in water with aid of heat. Remove from heat and add mercuric oxide slowly. Reheat until solution becomes dark purple. Remove from heat and plunge vessel into a basin of cold water until itis cool. Add 2-4 ml of glacial acetic acid per 100ml of solution and the stain is ready for use.

Acid Alcohol

Alcohol 70%	1000.0ml
Hydrochloricacid concentrated	010.0ml

1% Stock Alcohol eosin

Eosin Y, water soluble	1.0 ml
Distilled water	20.0 ml
Alcohol 95%	80.0 ml

Working eosin solution

Eosin solution	1 part
Alcohol, 80%	3 parts

Just before use, add 0.5 ml of glacial acetic acid to each 100ml of stain and stir.

Staining Procedure

- Remove paraffin wax with xylene - 5 minutes.
- Treat with absolute alcohol - 2 min.
- Immerse in 90% alcohol - 2 min.
- Immerse in 70% alcohol - 2 min.
- Immerse in 50% alcohol - 2 min.
- Immerse in water - 5 min.
- Immerse in hematoxylin - 5 to 10 min.
- 1% acid alcohol - 3 to 5 dips
- Immerse in running tap water for blueing- 10 min.
- Immerse in 1% eosin - 1 min.
- Wash in water.
- Dehydrate and clear in xylene.
- Mount in DPX

Results:

Nuclei	-	Blue black
Cytoplasm	-	Varying shades of pink
Muscle fibres	-	Deep pink red
Erythrocytes	-	Orange red
Fibrin	-	Deep pink

Histopathological examination of cystoscopic bladder biopsies and TURBT specimenswas carried out and the lesions were classified into various lesions on light microscopy.

RESULTS AND OBSERVATIONS

GENERAL CONSIDERATIONS

A total of 48 urinary bladder specimens were studied which included both Cystoscopic bladder biopsy and TURBT. This was a prospective study of urinary bladder specimens received in the histopathological section, Department of Pathology, Shri B M Patil Medical College and Research Centre from 1st November 2015 to 30th June 2017.

Table 5.1*: *Showing types of urinary bladder specimens included in study

Types of specimen	Number of cases	Percentage
Bladder biopsy	20	41.67
TURBT	28	58.33
Total	48	100

Fig 5.1*: *Pie chart showing types of urinary bladder specimens included in study

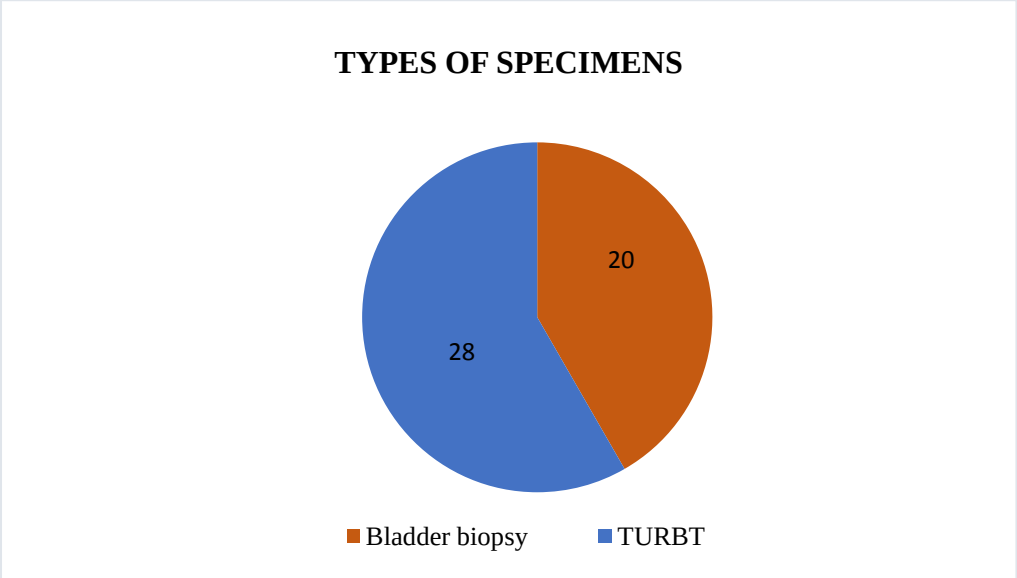


Table 5.2: Showing age wise distribution of all urinary bladder lesions

Age distribution (years)	Number of cases	Percentage(%)
<20	3	6.25
21-30	0	0
31-40	4	8.33
41-50	5	10.42
51-60	11	22.92
61-70	15	31.25
71-80	10	20.83
Total	48	100

As shown in above table, in the present study the age group was ranging from 2years to 80 years. There was clustering of cases between 51-80 years of age with maximum cases noted in 61-80 years constituting up to 52.08% of the entire samples among the study. The least number of cases were reported in younger age groups with no cases in 21-30 years group.

Fig5.2: Bar diagram showing age wise distribution of all urinary bladder lesions

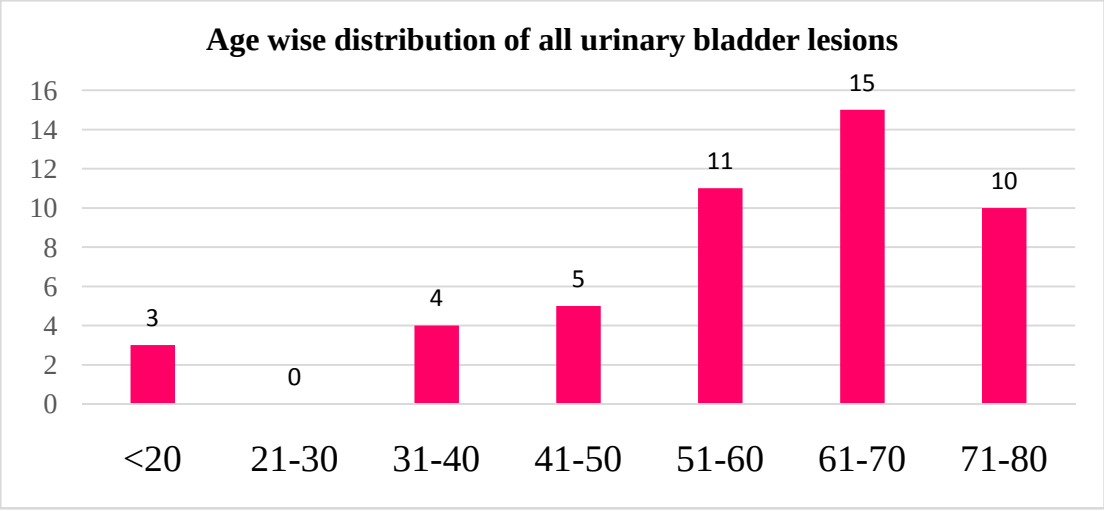


Table 5.3: Showing gender wise distribution of all urinary bladder lesions

Gender	Number of cases	Percentage(%)	
Males	29	60.42	M :F ratio = 1.5:1
Females	19	39.58	
Total	48	100	

As shown in above table, in the present study there were 29 males and 19 females constituting up to 60.42% and 39.58% respectively with a M:F ratio of 1.5:1.

Fig 5.3: Bar diagram showing gender wise distribution of all urinary bladder lesions

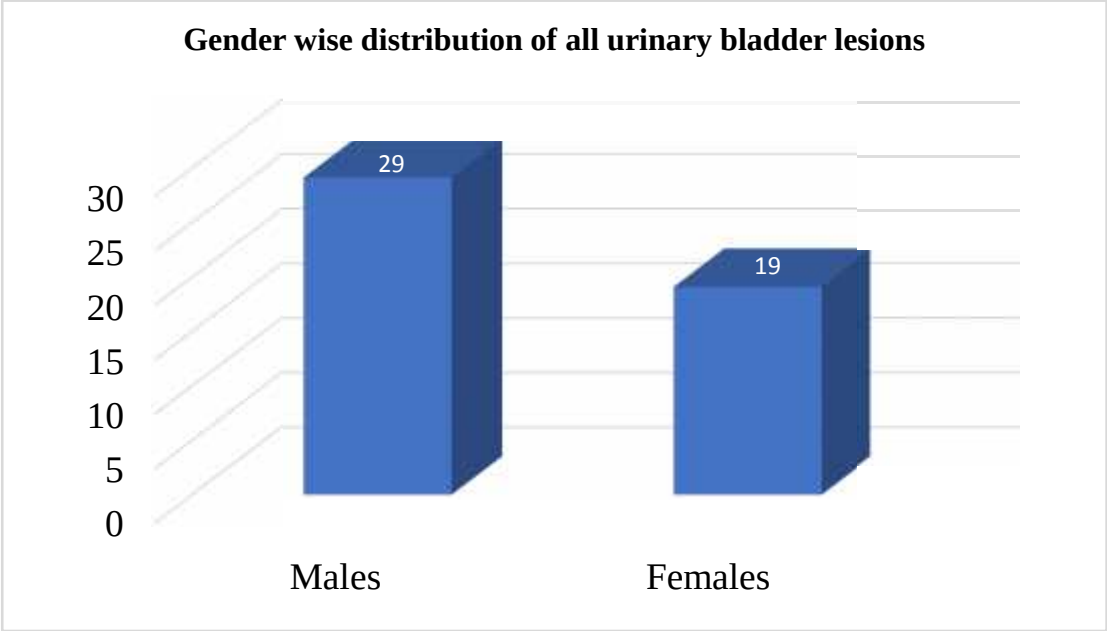
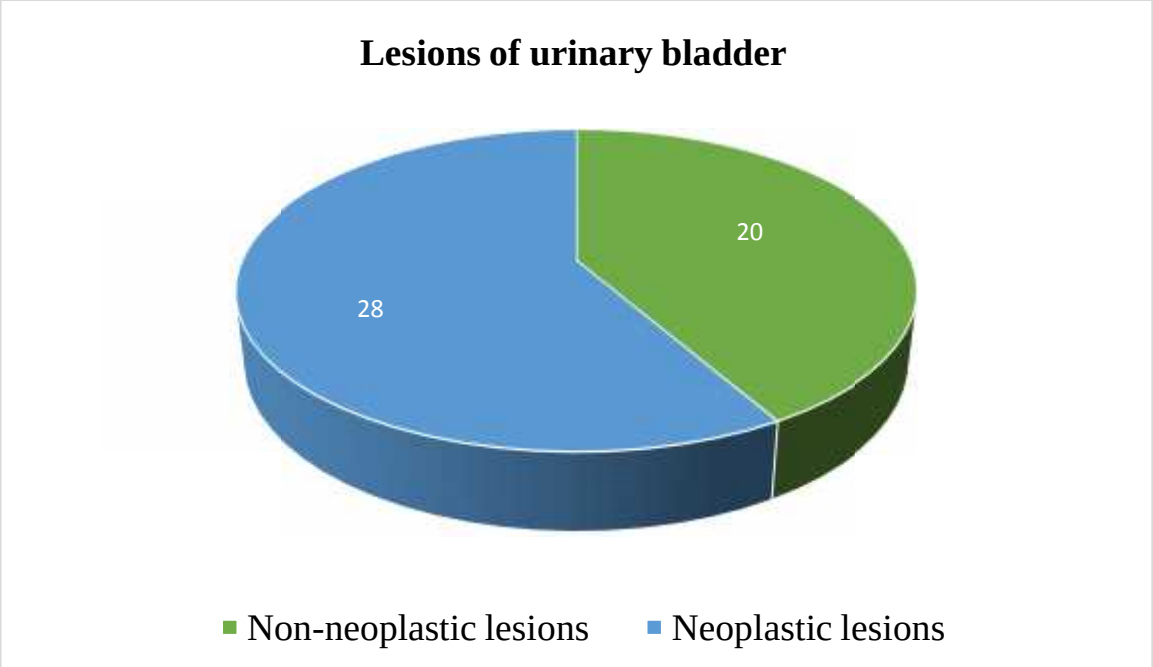


Table 5.4: Showing distribution of all lesions of urinary bladder

Type of lesion	**Number of cases**	**Percentage** (%)
Non-neoplastic lesions	20	41.67
Neoplastic lesions	28	58.33
Total	48	100

As shown in above table, in the present study there were 20(41.67%) non-neoplastic lesions and 28(58.33%) neoplastic lesions among all urinary bladder lesions.

Fig5.4*: *Pie chart showing distribution of all lesions of urinary bladder



NON-NEOPLASTIC LESIONS

Table 5.5: Showing age wise distribution of non-neoplastic lesions

Age group (years)	**Number of cases**	**Percentage** (%)
<20	3	15
21-30	0	0
31-40	4	20
41-50	3	15
51-60	3	15
61-70	5	25
71-80	2	10
Total	20	100

Fig5.5: Bar graph showing age wise distribution of non-neoplastic lesions

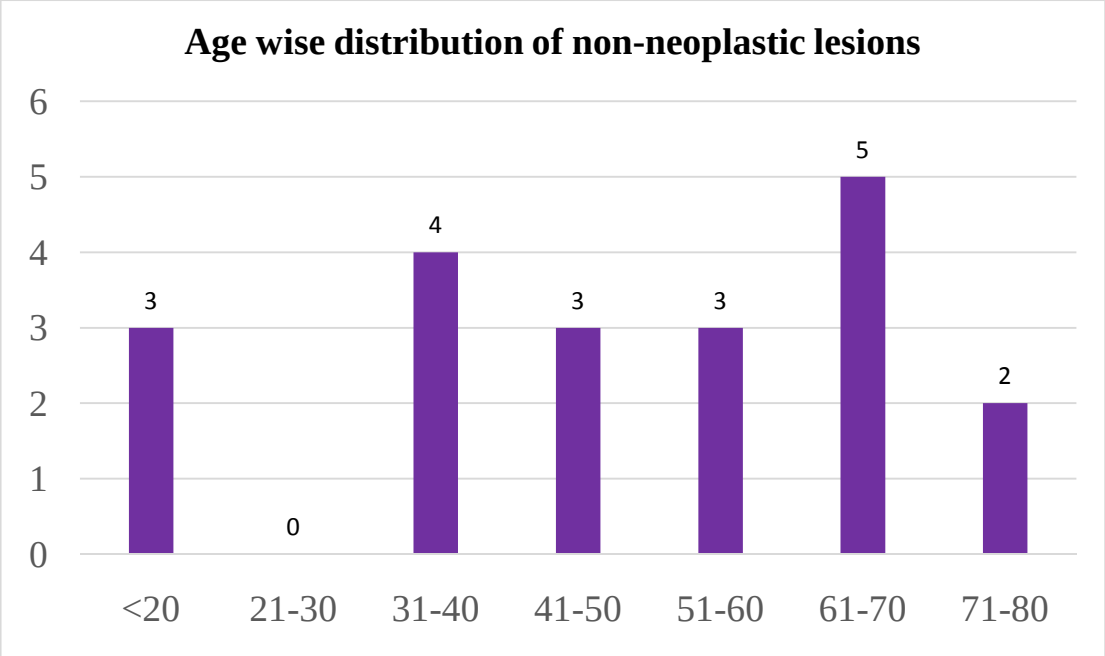


Table 5.6: Showing distribution of various non-neoplastic lesions

Type of lesion	**Number of cases**	**Percentage** (%)
Chronic nonspecific cystitis	12	60
Granulomatous cystitis	1	5
Acute on chronic cystitis	1	5
Polypoidal cystitis	1	5
Other types of cystitis	2	10
Variants of normal histology	3	15
Total	20	100

Table 5.6, showing distribution of various non-neoplastic lesions, among which chronic nonspecific cystitis was the predominant type constituting up to 60% of all cases. Other types of cystitis studied were one case each of eosinophilic and follicular cystitis. The variants of normal histology included in the study were one case each of cystitis cystica, cystitis glandularis and one case of fibroepithelial polyp which was present in a 2 year boy.

Fig5.6: Bar diagram showing distribution of various non-neoplastic lesions

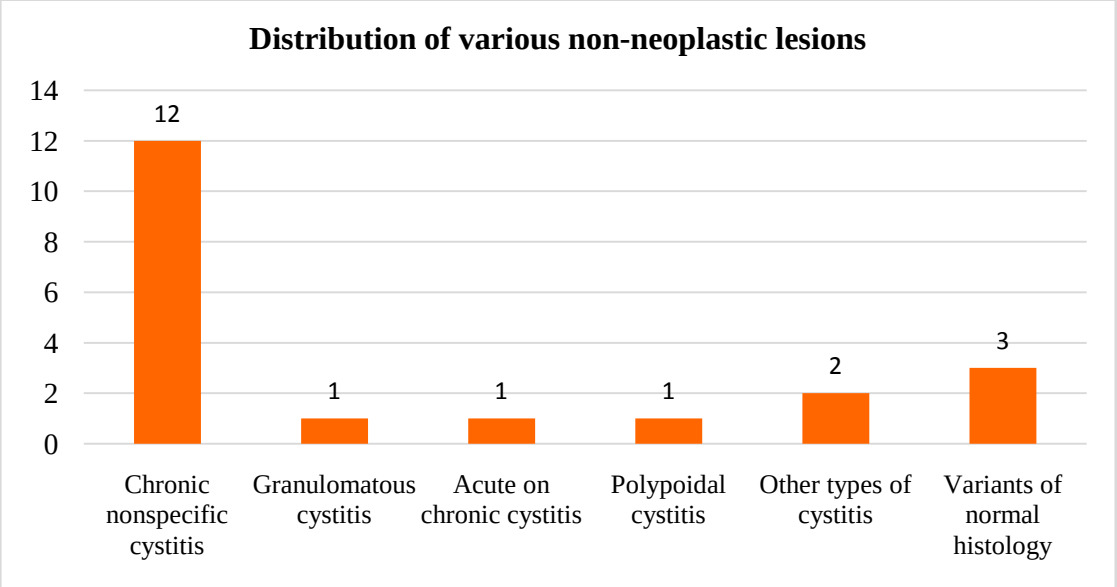
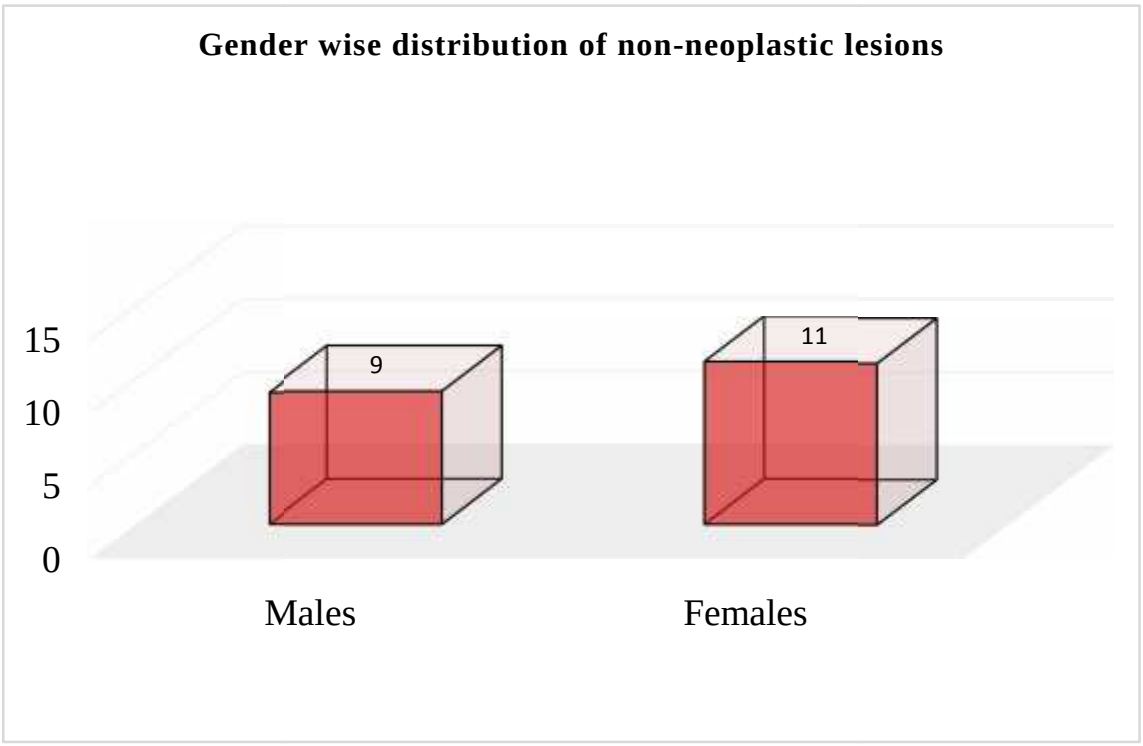


Table 5.7: Showing gender wise distribution of non-neoplastic lesions

Gender	**Number of cases**	**Percentage** (%)
Males	9	45
Females	11	55
Total	20	100

Table 5.7, showing genderwise distribution of all non-neoplastic lesions which is slightly more predominant among females than males.

Fig5.7:Bar diagram showing gender wise distribution of non-neoplastic lesions.



NEOPLASTIC LESIONS

Table 5.8: Showing age wise distribution of neoplastic lesions

Age group (years)	**Number of cases**	**Percentage** (%)
<20	0	0
21-30	0	0
31-40	0	0
41-50	2	7.14
51-60	8	28.57
61-70	10	35.71
71-80	8	28.57
Total	28	100

Table 5.8, showing age wise distribution of neoplastic lesions in the present study which is having a significant increase in the number of cases in the age group of 51 to 80 years together constituting 92.85% with nil cases observed in younger age group.

Fig 5.8: Bar diagram showing age wise distribution of neoplastic lesions

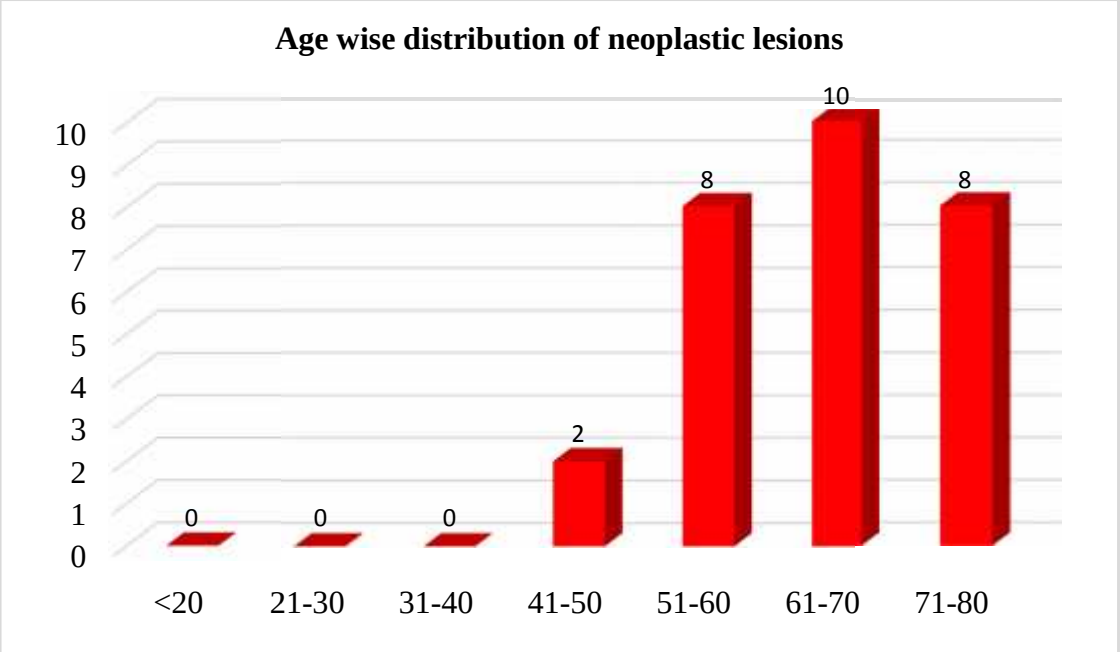


Table 5.9: Showing gender wise distribution of neoplastic lesions

Gender	**Number of cases**	**Percentage** (%)	
Males	20	71.43	M:F ratio for Neoplastic lesions is 2.5:1
Females	8	28.57	
Total	28	100	

Table 5.9, showing gender wise distribution of all neoplastic lesions with male predominance constituting 71.43% of all cases.M:F ratio for neoplastic lesions in the present study is 2.5:1.

Fig 5.9: Pie chart showing gender wise distribution of neoplastic lesions

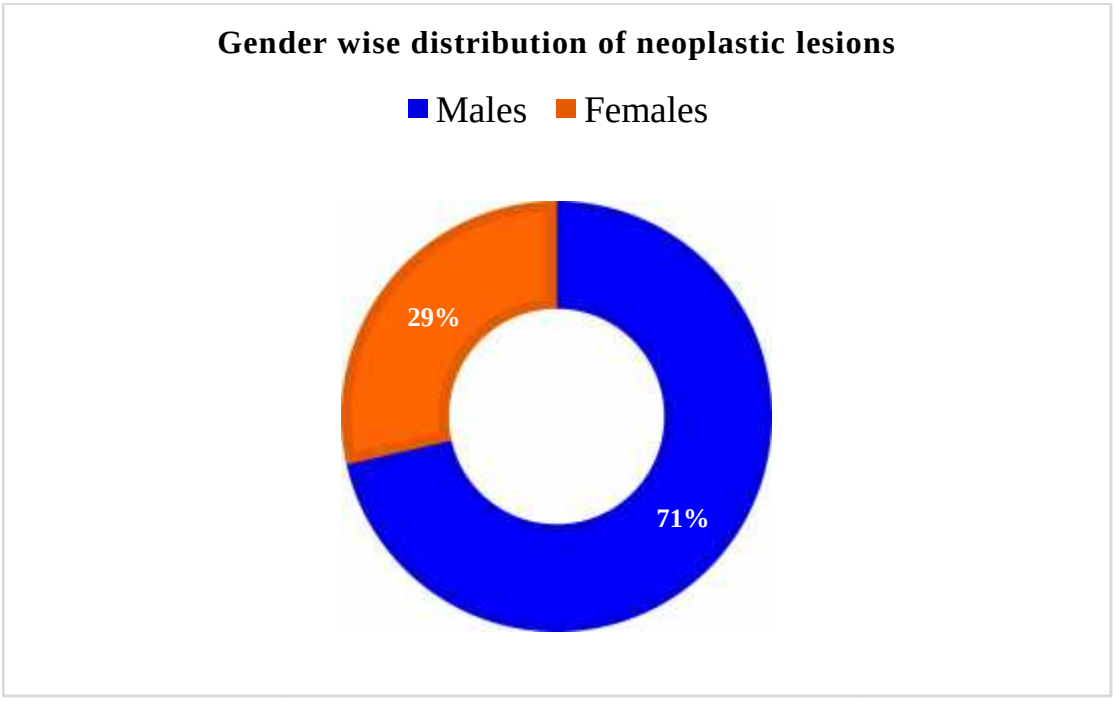


Table 5.10: Showing distribution of neoplastic lesions into various histomorphological categories

Type of lesion	**Number of cases**	**Percentage** (%)
Papillary urothelial neoplasm of low malignant potential	4	14.29
Non-invasive papillary urothelial carcinoma, low grade	5	17.86
Non-invasive papillary urothelial carcinoma, high grade	2	7.14
Invasive urothelial carcinoma	17	60.71
Total	28	100

Table 5.10, showing distribution of all neoplastic lesions into various histomorphological categories.IUC was more common among all lesions which included 7 cases of superficially invasive bladder cancer[11] (invasion upto lamina propria) and 10 cases of muscle invasive bladder cancer (invasion into muscularis propria).

Fig 5.10:Bar diagram showing distribution of neoplastic lesions into various histomorphological categories

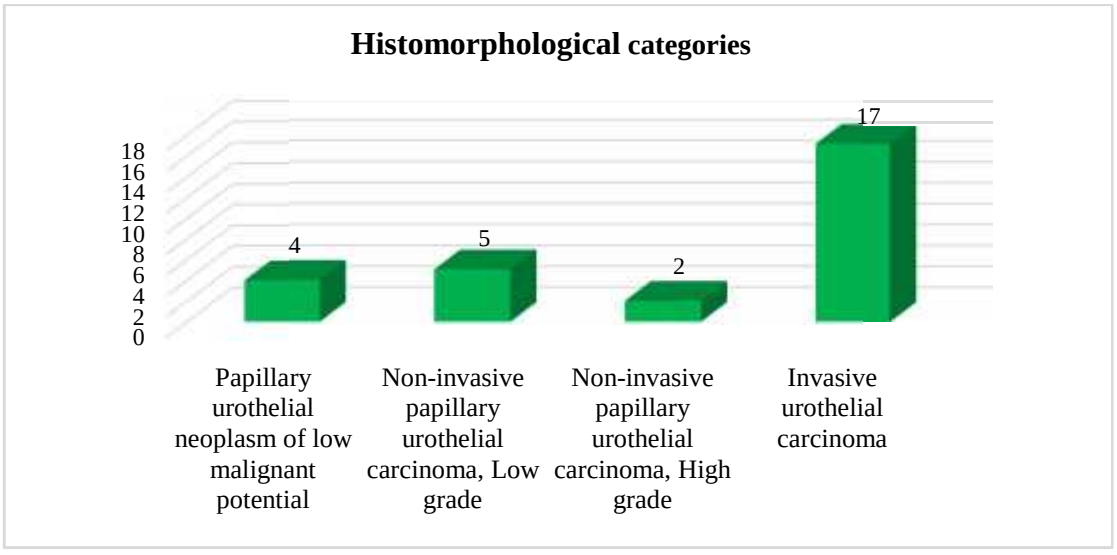


Table 5.11: Showing distribution according to microscopic extension of tumor

Microscopic extension	**Number of cases**	**Percentage** (%)
Non-invasive papillary carcinoma	11	39.29
Invasion upto lamina propria	7	25
Invasion upto muscularis propria	10	35.71
Total	28	100

Fig5.11: Bar diagram showing distribution according to microscopic extension of tumor.

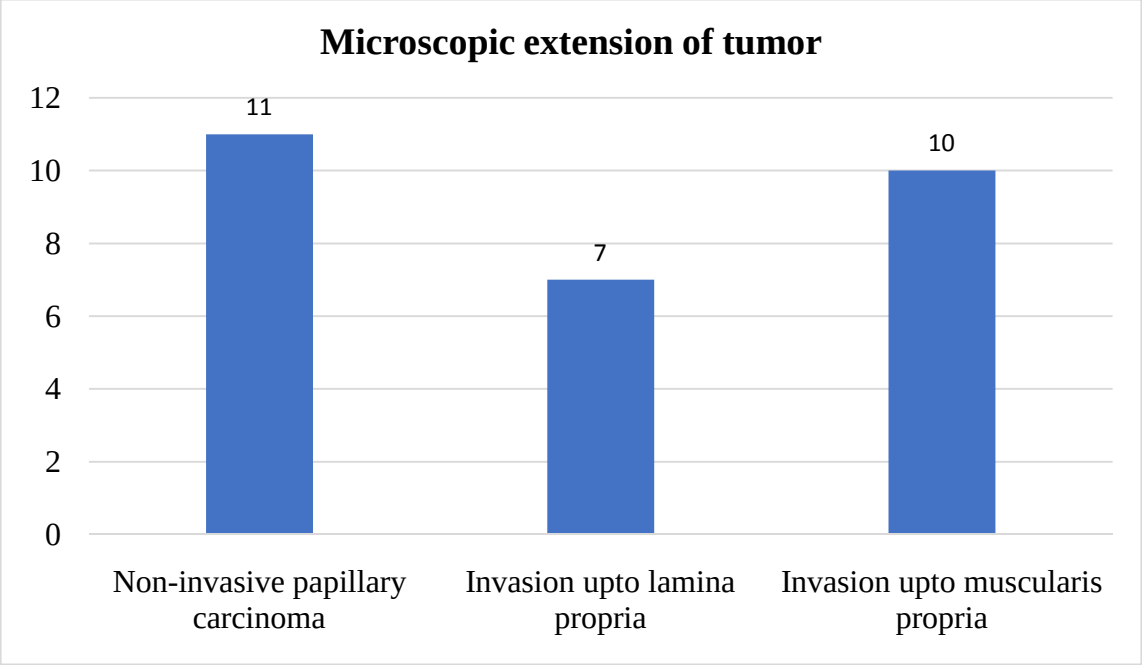


Table 5.12: Showing distribution according to non-muscle invasive and muscle invasive bladder cancer[10]

Category	Number of cases	Percentage (%)
Non-Muscle invasive bladder cancer	18	64.29%
Muscle invasive bladder cancer	10	35.71%
Total	28	100

Table 5.12 showing 18 cases of non-muscle invasive bladder cancers which included 11 cases of non-invasive and 7 cases of superficially invasive bladder cancer[11]and 10 cases of muscle invasive bladder cancer in the study.

Fig 5.12: Bar diagram showing distribution according to non-muscle invasive and muscle invasive bladder cancer

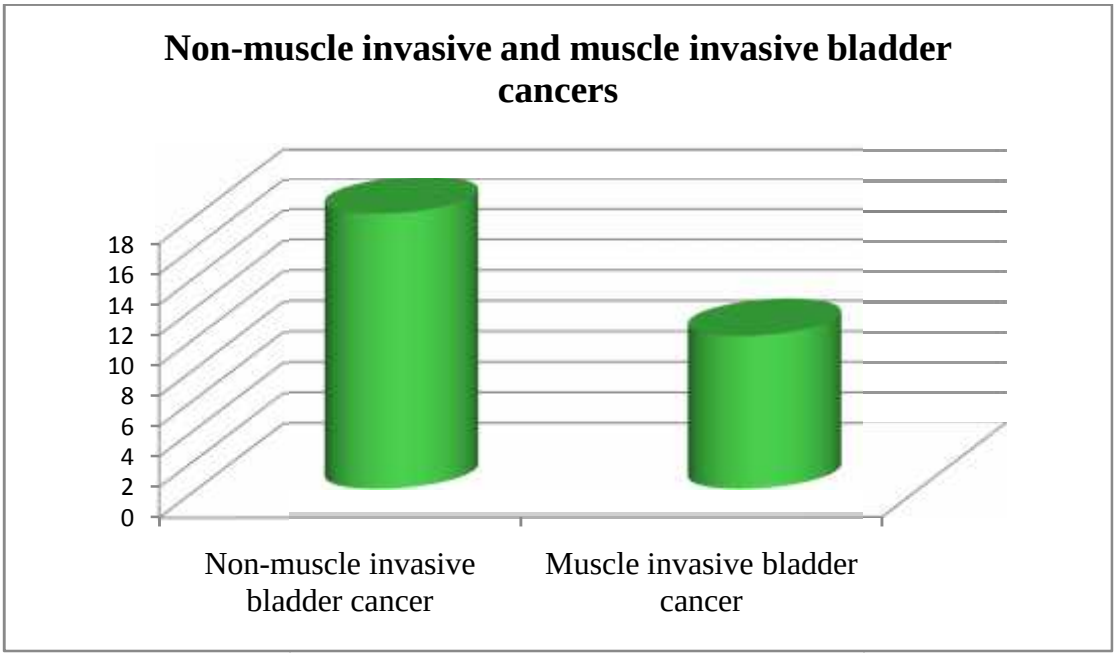


Table5.13:Showing distribution of non-neoplastic and neoplastic lesions according to age.

Age group (Years)	**Number of Non- neoplastic lesions**	(%)	**Number of Neoplastic lesions**	(%)	**Total cases**	(%)	**P-value**
<20	3	15	0	0	3	6.25	0.54*
21-30	0	0	0	0	0	0	
31-40	4	20	0	0	4	8.33	
41-50	3	15	2	7.14	5	10.42	
51-60	3	15	8	28.57	11	22.92	
61-70	5	25	10	35.71	15	31.25	
71-80	2	10	8	28.57	10	20.83	
Total	20	100	28	100	48	100	

Table 5.14: Showing distribution of non-neoplastic and neoplastic lesions according to gender

Gender	**Number of Non-neoplastic lesions**	%	**Number of Neoplastic lesions**	%	**Total**	%	**P-value**
Males	9	45	20	71.43	29	60.42	0.034*
Females	11	55	8	28.57	19	39.58	
Total	20	100	28	100	48	100	

The above table showing age wise and gender wise distribution of all non-neoplastic and neoplastic lesions. The P value for age wise distribution of both non-neoplastic and neoplastic lesions is 0.54. The P value for gender wise distribution of non-neoplastic and neoplastic lesions is 0.034 which is statistically significant.

GROSS IMAGES

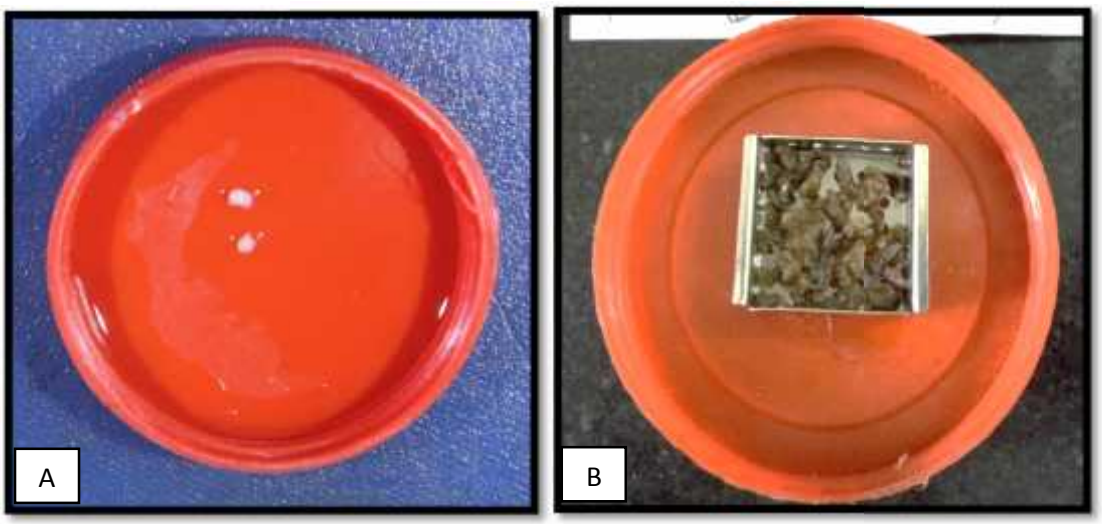


Fig 5.13: Gross photograph of A) Bladder biopsy and B) TURBT

MICROPHOTOGRAPHS OF NON-NEOPLASTIC LESIONS

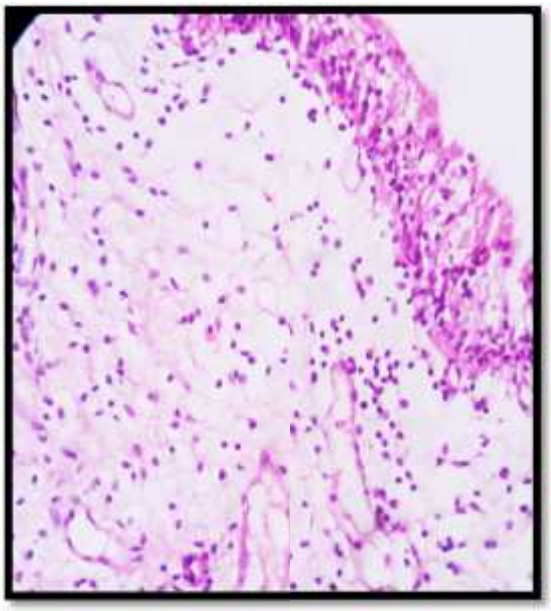


Fig 5.14: Chronic non-specific cystitis showing lymphoplasmacytic infiltrate in lamina propria [H&E, 400x]

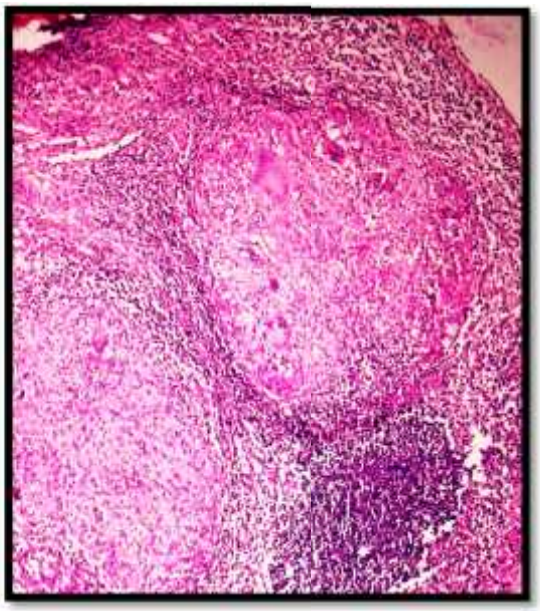


Fig 5.15: Granulomatous cystitis showing well-formed granulomas with langhans type of giant cell [H&E, 100x]

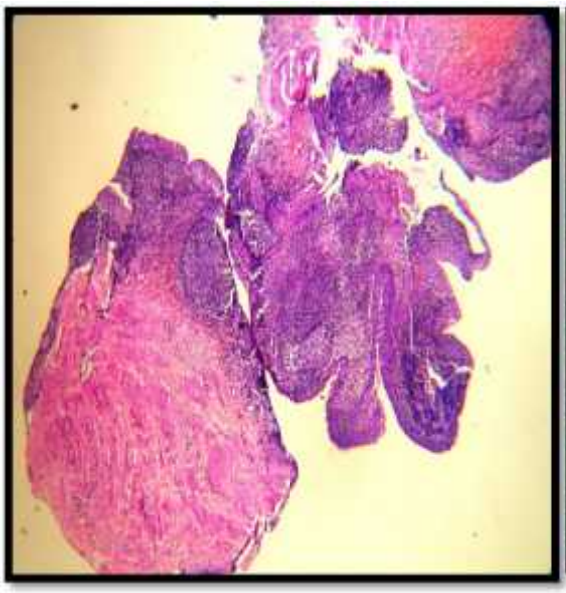


Fig 5.16: Follicular cystitis showing many lymphoid aggregates [H&E, 40x]

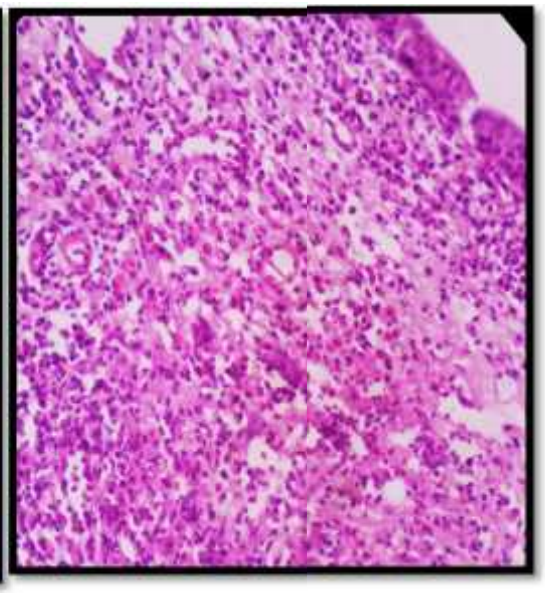


Fig 5.17: Eosinophilic cystitis showing diffuse eosinophilic infiltrate in lamina propria [H&E, 400x]

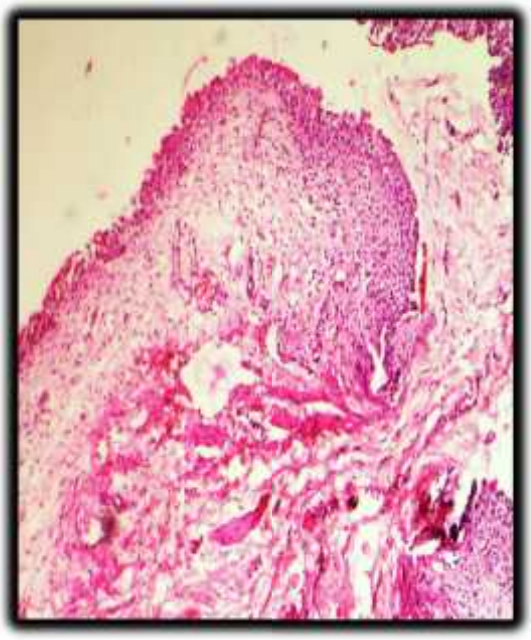


Fig 5.18: Polypoidal cystitis [H&E, 40x]

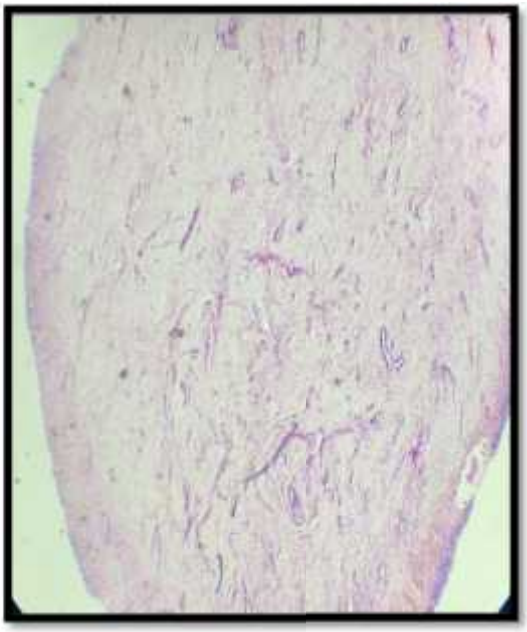


Fig 5.19: Fibroepithelial polyp[H&E, 40x]

MICROPHOTOGRAPHS OF VARIANTS OF NORMAL HISTOLOGY

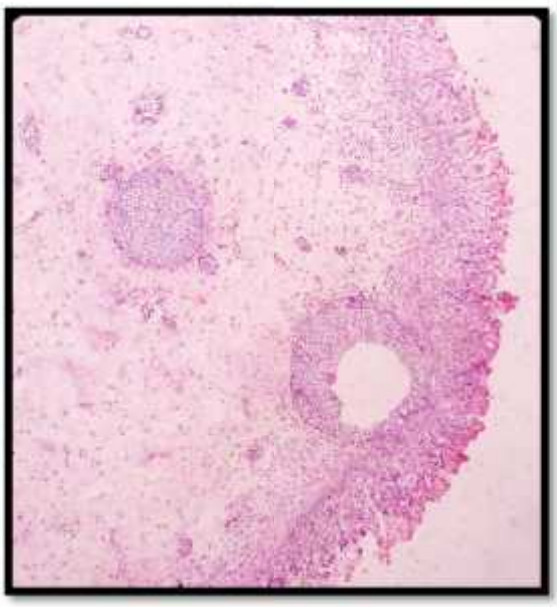


Fig 5.20: Cystitis cystica and Von Brunn nest [H&E, 40x]

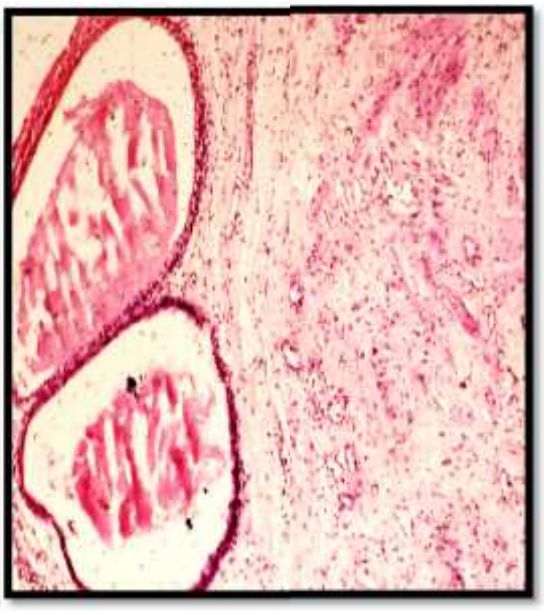


Fig 5.21: Cystitis glandularis [H&E, 100x]

MICROPHOTOGRAPHS OF NEOPLASTIC LESIONS

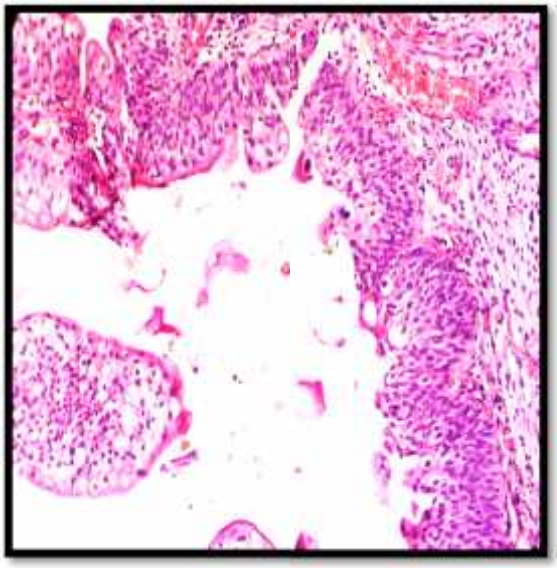


Fig 5.22: Papillary urothelial neoplasm of low malignant potential [H&E, 100x]

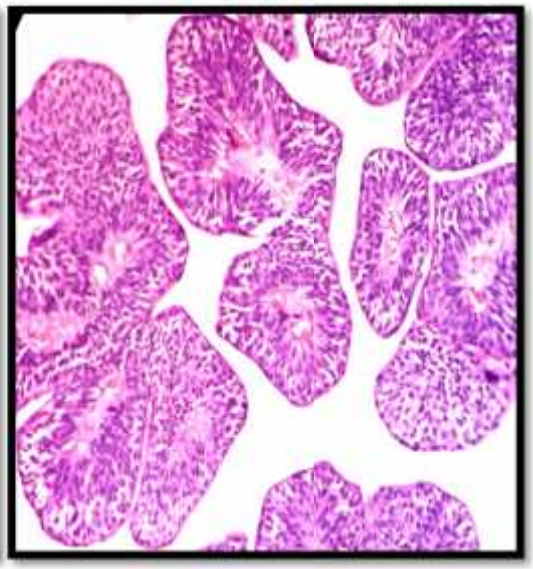


Fig 5.23: Non-invasive papillary urothelial carcinoma,low grade [H&E, 100x]

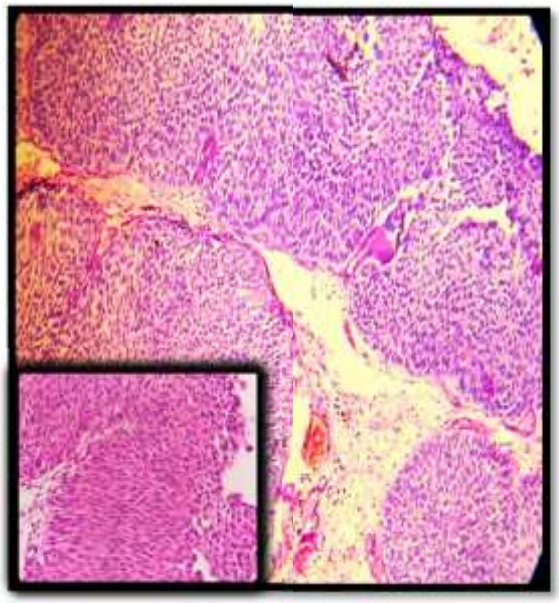


Fig 5.24: Non-invasive papillary urothelial carcinoma, high grade [H&E, 100x,400x]

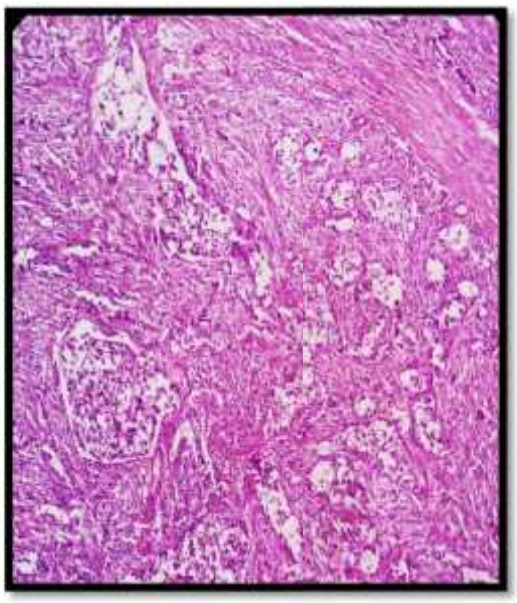


Fig 5.25: Invasive urothelial carcinoma, glandular variant showing invasion in to muscularis propria [H&E, 100x]

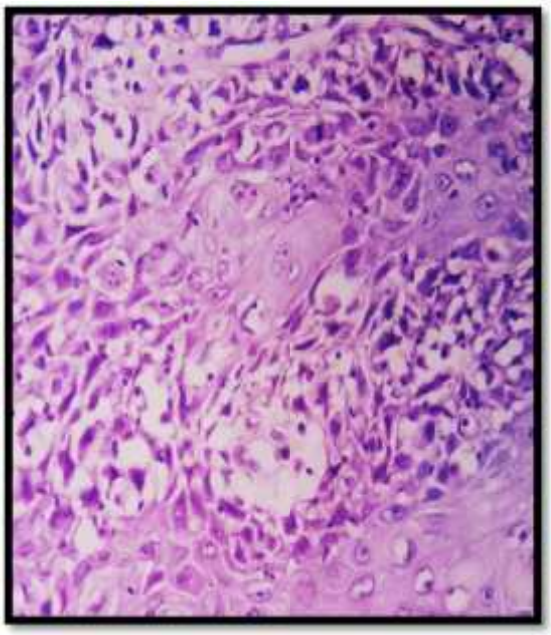


Fig 5.26, a :Invasive urothelial carcinoma, squamous differentiation [H&E, 400x]

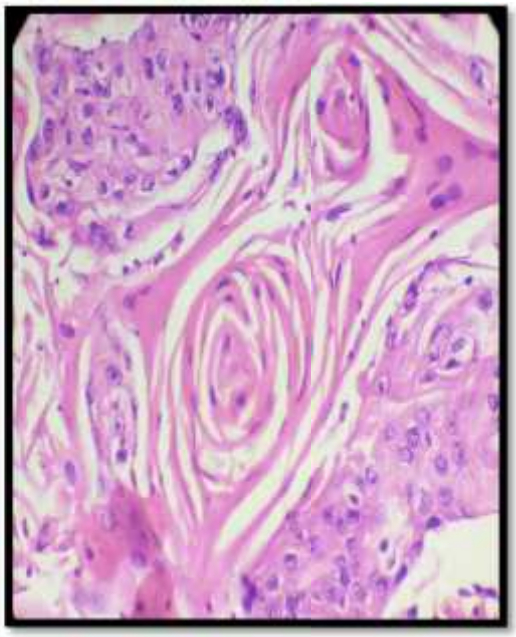


Fig 5.26, b: Invasive urothelial carcinoma, squamous differentiation – keratin pearl formation [H&E, 400x]

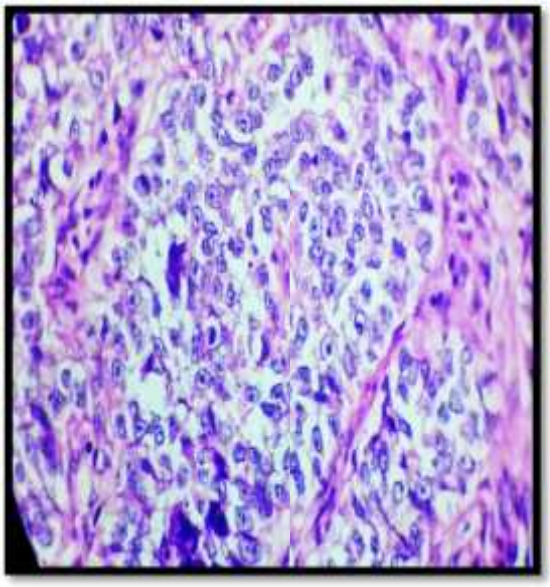


Fig 5.27: Invasive Urothelial Carcinoma, Clear cell variant [H&E, 400x]

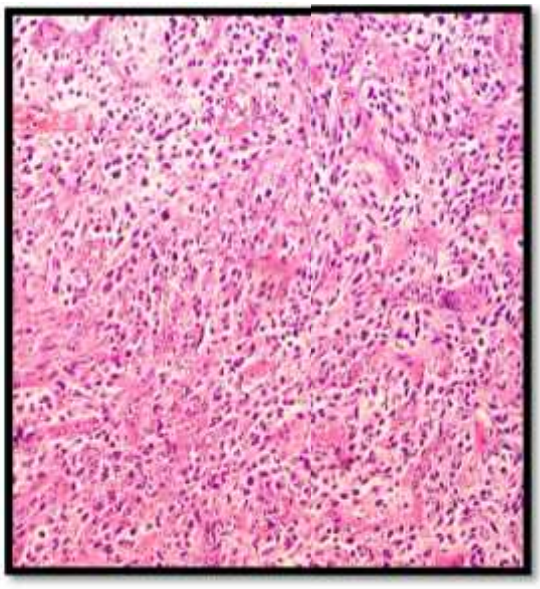


Fig 5.28: Invasive Urothelial Carcinoma, Sarcomatoid variant [H&E, 400x]

DISCUSSION

Diseases of the urinary bladder constitute an important source of clinical signs and symptoms, these are more disabling than lethal.[1] Both neoplastic and non-neoplastic lesions collectively accounts for notably high amount of morbidity and mortality.[4] Cystoscopy, which is a gold standard, primary diagnostic tool and TURBT being the most commonly practiced therapeutic and diagnostic procedure allows urologists to completely visualize bladder mucosa followed by sampling of the tissue for the histopathological examination.[4,50]

The present study includes 48 samples of urinary bladder lesions from patients visiting to Urology clinic with various complaints. Among this48 samples, 20 were cystoscopic biopsies and 28 were TURBT specimens. It includes 20 cases which were diagnosed as non-neoplastic conditions and 28 cases diagnosed as neoplastic conditions constituting to 41.67% and 58.33% respectively.

Out of 20 non-neoplastic lesions, 12 cases were chronic nonspecific cystitis, one case each of granulomatous, acute on chronic and polypoidal cystitis. Other types of cystitis included in the study were one case of eosinophilic and follicular cystitis each. Apart from this, it also included one case each of cystitis cystica, cystitis glandularis and fibroepithelial polyp.

Among the neoplastic lesions which were studied, urothelial neoplasms was the predominant type with a significant proportion of lesions seen in males. It included 4 cases of papillary urothelial neoplasm of low malignant potential, 5 were low-grade non-invasive urothelial carcinoma, 2 were high grade non-invasive urothelial carcinoma and 17 were invasive urothelial carcinoma which included7 cases of

superficially invasive bladder cancer and 10 cases of muscle invasive bladder cancer.Out of this, one case each with glandular and squamous differentiation along with other variants like clear cell variant, sarcomatoid variant were also studied.

Table 6.1*: *Distribution of all urinary bladder lesions in various studies

Study	**Year**	**Total Number of cases**	**Non-neoplastic lesions**	**Neoplastic lesions**	**Inadequate**
Shah PY *et al*[56]	2016	35	12 (34.28%)	23(65.71%)	0
Shruti HP*et al*[4]	2015	76	24(31.58%)	51(67.11%)	1(1.31%)
Srikousthubha *et al*[14]	2013	53	25(47.17%)	25(47.17%)	3(5.66%)
Grandhi B*et al*[57]	2016	48	16(33.33%)	32(66.67%)	0
Thapa R *et al*[58]	2017	87	29(33.33%)	58(66.67%)	0
Present study	2017	48	20(41.67%)	28(58.33%)	0

As shown in the above table, the present study included 48 cases. Out of these, 20(41.67%) cases were non-neoplastic lesions and 28(58.33%) cases were neoplastic lesions.

Table 6.2: Comparison showing age wise distribution of all urinary bladder lesions with various studies

Age groupin years	**Aparna C *et al*[19]**	**Grandhi B *et al*[57]**	**Shruti HP *et al*[4]**	**Present study**
<20	4(10.4%)	3(6.25%)	0	3(6.25%)
21-30	2(5.2%)	1(2.1%)	5(6.66%)	0
31-40	7(18.4%)	4(8.33%)	6(8%)	4(8.33%)
41-50	8(21%)	5(10.42%)	12(16%)	5(10.42%)
51-60	8(21%)	11(22.95%)	21(28%)	11(22.92%)
61-70	7(18.4%)	17(35.42%)	18(24%)	15(31.25%)
71-80	2(5.2%)	4(8.33%)	9(12%)	10(20.83%)
81-90	0	3(6.25%)	4(5.3%)	0
Total	38(100)	48(100)	75(100)	48(100)

As shown in the above table, there was clustering of cases between 51-60 years (22.92%), 61-70 years (31.25%) and 71-80 years (20.83%) of age groups, having 11,15 and 10 cases respectively in the present study. This constituted 75% of total cases studied. This finding was in concordance with study series by various authors like Aparna C *et al*[19], Grandhi B *et al*[57], Shruti HP*et al*[4].

Table 6.3: Comparison showing distribution of cystitis with various studies.

Study	Srikoustubah *et al*[14]	Shruti HP *et al*[4]	Present study
Chronic non-specific cystitis	15(71.4%)	19(79.2%)	12(60%)
Other forms of cystitis	6(28.6%)	5(20.8%)	5(25%)

As shown in table 6.3, in the present study 12 cases of chronic non-specific cystitis were diagnosed and 5 cases of other forms of cystitis were diagnosed like granulomatous, polypoidal, acute on chronic form, follicular and eosinophilic cystitis.These results were similar to study done by Srikoustubah *et al*[14] and Shruti HP*et al*[4] with chronic non-specific cystitis as predominant type studied.

Table 6.4: Gender wise distribution of neoplastic lesions in comparison with various studies.

Gender	Shah PY *et al*[56]	Srikoustubah *et al*[14]	Chinnaswamy R *et al*[59]	Shruti HP *et al*[4]	Present study
Males	16(69.57%)	21(84%)	127(81.41%)	39(79.6%)	20(71.43%)
Females	7(30.43%)	4(16%)	29(18.59%)	10(20.4%)	8(28.57%)
M:F ratio	2.29:1	5.25:1	4.38:1	3.9:1	2.5:1

This above table showing M:F ratio from various studies highlights the association bladder neoplasms and increased male susceptibility. Present study also had male preponderance with a M:F ratio of 2.5:1. However, there is wide range of M:F ratio observed between various studies ranging from least being observed is 2.29:1 in study

by Shah PY *et al*[56] to highest observed in study by Srikoustubah *et al*[14] having M:F ratio of 5.25:1. Smoking had a predominant role in development of Bladder cancer in males along with other factors like occupational carcinogens. However, this increased incidence among females in the present study could be explained by use of smokeless tobacco in the forms like gutka, paan, khaini or surti. And these contain many procarcinogenic agents like tobacco, betel nuts, saccharin, sugar coated fennel and heavy metals like silver.[59]

Table 6.5: Showing distribution of various urothelial neoplasms in comparison with other studies.

Studies	**Shah PY *et al*[56]**	**Shruti HP *et al*[4]**	**Laishram *et al*[60]**	**Present study**
Papilloma	0	2(4%)	2(4.44%)	0
Papillary urothelial neoplasm of low malignant potential	3(15.79%)	3(6.12%)	1(2.22%)	4(14.29%)
Non-invasive papillary urothelial carcinoma, Low grade	6(31.58%)	17(34.6%)	14(31.11%)	5(17.86%)
Non-invasive papillary urothelial carcinoma, High grade	1(5.26%)	14(28.5%)	9(20%)	2(7.14%)
Invasive urothelial carcinoma	9(47.37%)	13(26.5%)	19(42.22%)	17(60.71%)
Total	19	49	45	28

As shown in table 6.5, IUC was predominant type among the urothelial neoplasms constituting around 60% of all cases in the present study which was more than in studies done by Shah PY *et al*[56]and Laishram *et al*[60]. However, they also reported IUC as the predominant histological type of urothelial carcinoma.

Table 6.6: Showing various differentiations among invasive urothelial carcinoma in comparison with other studies.

Differentiation	Goyal VK *et al*[2]	Shruti HP *et al*[4]	Present study
Nil	82(92.13%)	13(86.67%)	13(76.48%)
Squamous	5(5.61)	1(6.67%)	1(5.88%)
Glandular	1(1.12%)	0	1(5.88%)
Nested	1(1.12%)	0	0
Clear cell	0	0	1(5.88%)
Sarcomatoid	0	1(6.67%)	1(5.88%)

As shown in above table, invasive urothelial carcinoma without any differentiation was the most predominant type comprising 3/4th of the total cases in present study and also in various other studies. The other variants studied were invasive urothelial carcinoma with squamous and glandular differentiation, along with clear cell and sarcomatoid variant.

Table 6.7: Showing microscopic extent of invasion among urothelial neoplasm in comparison with other studies

Microscopic extent of invasion	**Rajeshwari K *et al*[18]**	**Laishram *et al*[60]**	**Present study**
Non-invasive papillary carcinoma	20(22.22%)	14(53.85%)	11(39.29%)
Invasion up to lamina propria	49(54.44%)	4(15.38%)	7(25%)
Invasion up to musclaris propria	21(23.33%)	8(30.77%)	10(35.71%)
Total	90	26	28

Asshown in above table, the non-invasive papillary carcinoma cases were 39.29% where in there was no breach in the basement membrane. Invasion up to lamina propria were seen in 25% of cases, 35.71% were having invasion of muscularis propria in the present study.

CONCLUSION

Urinary bladder lesions are most frequently encountered by surgical pathologists and are heterogenous. Both benign and malignant lesions are well documented but latter being more common. Many of these are more common in elderly people with male predilection and are often associated with smoking. However, there is increasing incidence in the female population in the recent years which might be due to increased exposure to environmental and occupational carcinogensalong with exposure to smokeless tobacco.

Majority of bladder cancers are urothelial in origin representing 90% of malignancies with this origin. Majority of them being non-muscle invasive urothelial carcinomas which included papillary urothelial neoplasm of low malignant potential, non-invasive papillary urothelial carcinoma, low grade and high grade. However,muscle invasive urothelial carcinomas without any differentiation are also frequently encountered. IUC with squamous and glandular differentiation were also studied which are reported in 20% and 16% of the cases respectively. Other variants like sarcomatoid and clear cell variant were also studied which are extremely rare and often carry bad prognosis.Other neoplastic lesions studied also

Identifying the extent of invasion by microscopic examination constitutes an important aspect in urothelial carcinomas.Invasion of muscularis mucosa and muscularis propria has to be differentiated carefully as the prognostic and therapeutic aspects are entirely different in both of them. In cases of dilemma IHC is most helpful.Awareness regarding the various histological features of these lesions, their neoplastic potential, risk of recurrence and possible pitfalls helps for accurate diagnosis.

Though bladder neoplasms are common there are a number of benign lesions that can manifest as focal mass and mimic malignancy. Some of such entities are papillomas and urothelial proliferation of uncertain malignant potential. Other lesions like cystitis

glandularis, cystitis cystica and von brunn nests which are actually considered to be variants of normal histology should also be carefully distinguished from malignant lesions.

SUMMARY

- The present prospective study was undertaken in Department of Pathology, Shri B M Patil Medical College and Research Centre from November 2015 to June 2017to studythehistopathological spectrum of urinary bladder lesions in TURBT and cystoscopic biopsies, incidence of various non-neoplastic and neoplastic lesions, age and sex distribution of various urinary bladder lesions.
- Total of 48 samples from urinary bladder in the form of cystoscopic biopsy and TURBT were studied.
- All the samples were fixed in 10% formalin and processed according to standard protocol then stained with H&E followed by microscopic examination.
- Among 48 samples, 20 were Cystoscopic biopsy and 28 were TURBT which included patient ranging from 2years to 80years.
- Out of 48 cases, 20 were non-neoplastic lesions and 28 were neoplastic lesions. Among non-neoplastic lesions, cystitis and variants of normal histology were studied which included chronic nonspecific cystitis, granulomatous, acute on chronic, polypoidal, eosinophilic and follicular cystitis along with cystitis cystica, cystitis glandularis and fibroepithelial polyp.
- Malignant lesions were seen in the age group of 41-80 years with peak incidence in 6^{th} and 7^{th} decade. Out of 28 neoplastic lesions, 20 were seen in male patients, 8 were seen in female patients with a M:F ratio of 2.5:1.
- Out of 28 cases, 11 were non-invasive urothelial neoplasms which included 4 cases of PUNLMP, 5 were NIPUC-LG, 2 were NIPUC-HG. Among IUC,7 were superficially invasiveand 10 were muscle invasive urothelial carcinoma, which included invasive carcinoma without any differentiation and one cases each of squamous, glandular differentiation, clear cell and sarcomatoid variants.

LIMITATIONS OF THE STUDY

The presentstudy tried to elaborate the histopathological spectrum of lesions in urinary bladder with cystoscopic biopsies and TURBT specimens. Evaluation of high grade and invasive carcinomas with immunohistochemical studies would have further helped in accessing the level of invasion accurately which is helpful from therapeutic aspects. Inclusion of the above measure would have improved the sensitivity of the diagnosis.

BIBLIOGRAPHY

1. Epstein JI, Lotan TL. The Lower Urinary Tract and Male Genital System. In: Kumar V, Abbas AK, Aster JC, editors. Robbins and Cotran Pathologic Basis of Diseases.9th ed. Faridabad: Elsevier, 2014; p. 961-9.
2. Goyal VK, Vyas SP, Kothari DC. Spectrum of Lesions in Urinary Bladder Biopsies :Histopathological Study. Int J Dent Med Res. 2015;1(6):42–6.
3. Pudasaini S, Subedi N, Prasad KBR, Rauniyar SK, Josi BR,Bhomi KK. Cystoscopic bladder biopsies :A histopathological study. Nepal Med Coll J. 2014;16(1):9–12.
4. Shruthi.HP, Rangaswamy.R. Sectrum of Lesions in Urinary Bladder Biopsies-A Histopathological Study.IJHSR.2015 May;5(5):144-52
5. Felix AS, Soliman AS, Khalad H, Zaqhloul MS, Banerjee M, El-Baradie M*et al*. The changing patterns of bladder cancer in Egypt over the past 26 years. Cancer Causes Control. 2008 May;19(4):421–9.
6. Young B, Woodford P, Dowd GO.Wheater's Functional Histology. 6th ed. USA: Elsevier Health Sciences, 2014;p. 292-317.
7. Standring S. Bladder, Prostate and Urethra. Gray's Anatomy. 40th ed. Spain:Elsevier,2008; p.1245-50.
8. Rani kumar.Urogenital system. Textbook of human Embryology. New Delhi: I.K. International publishing House Pvt. Ltd,2008; p. 159-61
9. Young RH. Non neoplastic disorders of the urinary bladder. In: Bostwick DG, Cheng L editors. Urologic surgical pathology. 3rd ed. Philadelphia: Elsevier, 2014;p. 196-226.

10. Wood DP. Tumors of Bladder. In: WeinJA, Kavoussi RL, Partin WA, Peters CA editors. Campbell-Walsh Urology.11th ed. China: Elsevier, 2016; p. 2184-204.
11. Reuter VE, Ahmadie HA. Urothelial Tract: Renal Pelvis, Ureter, Urinary Bladder and Urethra. In Mills SE editor. Sternberg's Diagnostic Surgical Pathology. 6th ed. China: Wolters Kluwer, 2015;p. 2049-89.
12. Urinary System. In: Eroschenko VP editor. DiFiore's Atlas of Histology with Functional Correlations. 12th ed. Philadelphia: Wolters Kluwer, 2013; p. 442-5.
13. Buck EG. Polypoidal cystitis mimicking transitional cell carcinoma. J Urol. 1984 May;131(5):963.
14. Srikousthubha, Sukesh, Raghuveer CV, Hingle S. Profile of Lesions in Cystoscopic Bladder Biopsies: A Histopathological Study. J Clin Diagn Res. 2013 Aug;7(8):1609-12.
15. Teegavarapu PS, Sahai A, Chandra A, Dasgupta P, Khan MS. Eosinophilic cystitis and its management. Int J Clin Pract. 2005 Mar; 59(3):356-60.
16. Chai D. Eosinophilic cystitis and hematuria: Case report of a rare dissease and common presentation. Int J Surg Case Rep. 2016;24:43-5.
17. Antoni S, Ferlay J, Soerjomataram I, Znaor A, Jemal A, Bray F. Bladder Cancer Incidence and Mortality: A Global overview and Recent trends. Eur Urol. 2017 Jan;71(1):96-108
18. Rajeshwari K, Dravid NV, Karibasappa GN, Patil A. Histomorphological Profile of Lesions in Cystoscopic Bladder Biposies-A prospective Study in North Maharashtra. Int Clin Pathol J. 2016;3(1):1-9

19. Aparna C, Thumma RR, Devi CP, Vanapalli SVRLJ, Mounika TDN. Histopathological Spectrum of Urothelial lesions- Experience of A Single Tertiary Care Institute. IJCMR. 2016;3(6):1731-3
20. Torre LA, Bray F, Siegel RL, Ferlay J, Tieulent JL, Jemal A. Global Cancer Statistics, 2012. CA Cancer J Clin. 2015;65:87-108.
21. National centre for disease informatics & research. National cancer registry programme. Three-year report of population based cancer registries: 2012-2014.[document on the internet]. Indian council of medical research. [cited on 2017 Sept 16]Available from:icmr.nic.in/ncrp/pbcr_2012-14/ALL_CONTENT/PDF_Printed_Version/Chapter7_Printed.pdf
22. Mubarak M, Kazi JI, Hashmi A, Hussain M, Naqvi SA, Rizvi SAH. Urinary Bladder Tumors in Southern Pakistan: A Histopathological Perspective. Middle East J Cancer. 2014 July;5(3):167–73.
23. Kumar MU, Yelikar BR. Spectrum of Lesions in Cystoscopic Bladder Biopsies- A Histopathological Study. Al Ameen J Med Sci. 2012;5(2):132-6.
24. Matalka I, Bani HK, Shota A, Bani HO, Bani HI. Transitional cell carcinoma of the urinary bladder: a clinicopathological study. Singapore Med J.2008;49(10):790-4.
25. Humphrey PA, Moch H, Cubilla AL, Ulbright TM, Reuter VE. The 2016 WHO Classification of tumours of the Urinary System and Male Genital Organs- Part B: Prostate and Bladder Tumours. Eur Urol. 2016 July;70(1):110-5.
26. Beltran AL, Sauter G, Gasser T, Hartmann A, Drager BJS, Helpap B.et al. Infiltrating urothelial carcinoma. In: Eble JN, Sauter G, Epstein JI, Sesterhenn IA editors. WHO classification of Tumors, Pathology and Genetics Tumors of

the Urinary system and male genital organs. 3rded. France: IARC Press, 2004; p. 93-109.

27. Grignon DJ. The current classification of urothelial neoplasms. Mod. Pathol. 2009;22(SUPPL 2):S60-9.
28. Eble JN, Grignon DJ, Young RH. Tumors of the urinary bladder and urethra. In: Fletcher CDM editor. Diagnostic histopathology of tumors. 4th ed. Philadelphia: Elsevier, 2013;p. 610-48.
29. Bochner BH, Hansel DE, Efstathiou JA, Konety B, Lee CT, Mckiernan JM *et al*. Urinary Bladder.In: Amin MB editor. AJCC Cancer Staging Manual. 8th edition. Switzerland: Springer, 2017;p. 757-65.
30. Amin MB. Histological variants of urothelial carcinoma: diagnostic, therapeutic and prognostic implications. Mod. Pathol. 2009 Jun;22(2):S96-S118.
31. Lui Y, Bui MM, Xu B. Urothelial Carcinoma With Squamous Differentiation Is Associated With high Tumor Stage and Pelvic Lymph-Node Metastasis. Cancer Control.2017Jan;24(1):78-81.
32. Chalasani V, Chin JL, Izawa JI. Histologic variants of urothelial bladder cancer and nonurothelial histology in bladder cancer. Can Urol Assoc J.2009December;3(6):S193-8.
33. Knez VM, Barrow W, Lucia MS, Wilson S, Rosa FGL. Clear cell urothelial carcinoma of the urinary bladder: a case report and review of literature. J Med Case Rep. 2014;8:275.
34. Comperat E. The WHO Classification 2016 of Tumours in the Urinary System and Male Genital Organs and Impact on the Bladder Cancer. Clin Oncol. 2017;2(1235):1-2.

35. Grignon DJ, El-Bolkainy MN, Drager BJS, Simon R, Tyczynski JE. Squamous cell carcinoma. In: Eble JN, Sauter G, Epstein JI, Sesterhenn IA editor. WHO classification of Tumors, Pathology and Genetics Tumors of the Urinary system and male genital organs. 3edition. France, IARC Press, 2004; p. 124-7.
36. Ayala AG, Tamboli P, El-Bokainy MN, Schoenberg MP, Oliva E, Sidransky D *et al*.Adenocarcinoma. In: Eble JN, Sauter G, Epstein JI, Sesterhenn IA editor. WHO classification of Tumors, Pathology and Genetics Tumors of the Urinary system and male genital organs. 3edition. France, IARC Press, 2004; p. 128-30.
37. Quan J, Pan X, Jin L, He T, Hu J, Shi B *et al*.Urachal carcinoma: Report of two cases and review of literature. Mol Clin Oncol. 2017 Jan; 6(1):101-4.
38. Miller EM, Sun Y, Richardson I, Frimer M. Vesical clear cell adenocarcinoma arising from endometriosis: A Mullerian tumor, indistinguishable from ovarian clear cell adenoacarcinoma. Gynecol oncol Rep. 2016 Nov;18:8-10
39. Kouba E, Cheng L. Neuroendocrine Tumors of the Urinary Bladder According to the 2016 World Health Organisation Classification: Molecular and Clinical Characteristics. Endocr Pathol. 2016 Sep;27(3):188-99.
40. Agaimy A, Hartmann A. Mesenchymal tumors of the urinary bladder. Pathologe. 2016 Feb;37(1):61-70.
41. Bates AW, Norton AJ, Baithun SI. Malignant lymphoma of the urinary bladder: a clinicopathological study of 11 cases. J Clin pathol. 2000 June;53(6):458-61.
42. National cancer institute [image on the internet]. C2013 [updated 2017 April 27; cited2017 Aug 20].Available from:

http://cancer.gov/types/bladder/patients/bladder-treatment-pdq#section/_109

43. Desai S, Lim SD, Jimenez RE, Chun T, Keane TE, McKenney JK*et al*. Relationship of Cytokeratin 20 and CD44 protein expression with WHO/ISUP Grade in pTa and pT1 Papillary Urothelial Neoplasia. Mod. Pathol. 2000;13(12):1315-23.
44. Mumtaz S, Hashmi AA, Hasan SH, Edhi MM, Khan M. Diagnostic utility of p53 and CK20 immunohistochemical expression grading urothelial malignancies. Int Arch Med. 2014;7:36.
45. Rajcani J, Kajo K, Adamkov M, Moravekova, Lauko L, Felcanova D *et al.*Immunohistochemical characterization of urothelial carcinoma. Bratisl Lek Listy. 2013;114(8):431-8.
46. Council L, Hameed O. Differential expression of immunohistochemical markers in bladder smooth muscle and myofibroblasts, and the potential utility of desmin, smoothelin and vimentin in staging of bladder carcinoma. Mod pathol. 2009 May;22(5):639-50.
47. Paner GP,Shen SS, Lapetino S, Venkataraman G, Barkan GA,Quek ML et al. Diagnostic utility of antibody to smoothelin in the distinction of muscularis propria from muscularis mucosae of the urinary bladder: a potential ancillary tool in the pathological staging of invasive urothelial carcinoma. Am J Surg Pathol. 2009 Jan;33(1):91-8.
48. Samplaski MK, Jones JS. Two centuries of cystoscopy: the development of imaging, instrumentation and synergistic technologies. BJU Int. 2009 Jan;103(2):154-8.
49. Wuilleumier J, Point D, Fooks H, Zaslau S. The History of Cystoscopy in Urology. IJU. 2015;14(1):1-8.

50. Jecu M, Geavlete B, Multescu R, Stanescu F, Moldoveanu C, Adou L et al. NBI cystoscopy in routine urological practice- from better vision to improve therapeutic management. J Med Life. 2014 June 15;7(2):282-6

51. Breda A, Territo A, Guttilla A, Sanguedolce F, Manfredi M, Quaresima L et al. Correlation Between Confocal Laser Endomicroscopy (Cellvizio®) and Histological Grading of Upper Tract Urothelial Carcinoma: A Step Forward for a Better Selection of Patients Suitable for Conservative Management. Eur Urol Focus- press release .2017 June 4.
http://dx.doi.org/10.1016/i.euf.2017.05.008

52. Kharchenko S, Adamawicz J, Wojtkowski M, Drewa T. Optical coherence tomography diagnostics for onco-urology. Review of clinical perspectives. Cent European J Urol.2013;66(2):136-41.

53. Barjuk M. Transurethralresection of Non-muscle invasive Bladder Cancer. European Urology Supplements 8. 2009;542-8.

54. Jurewicz M, Soloway MS. Approaching the optimal transurethral resection of a bladder tumor. Turk J Urol.2014 Jun;40(2):73-7.

55. Dorotta I, Basali A, Ritchey M, O'Hara JF, Sprung J. Transurethral Resection Syndrome After Bladder Perforation. Anesth Analg. 2003;97:1536-8.

56. Shah PY, Nanavati M, Patel RG, Goswami HM. Spectrum of lesions in urinary bladder- A histopathological study. Int J Cur Res Rev.2016; 8(4):19-24.

57. Grandhi B, Byna SSR, Shanthi V, Vydehi BV, Rao NM, Goel A. Histopathological Spectrum of Urothelial Lesions. IOSR-JDMS. 2016;15(6):4-7.

58. Thapa R, Lakhey M, Bhatta AD. Spectrum of histomorphological diagnosis in Cystoscopic bladder biopsies. J Pathol of Nepal. 2017;7:1062-5.
59. Chinnaswamy R, Krishnamoorthy S, Joseph L, kumaresan N, Ramanan V. Clinico-pathological Study of Bladder Cancer in a Tertiary Care Centre of South India and Impact of Age, Gender, and Tobacco in Causing Bladder Cancer: A Single Centre Experience. Int J Sci Stud.2016; 3(10):72-7.
60. Laishram RS, Kipgen P, Laishram S, Khuraijam S, Sharma DC. Urothelial Tumors of the Urinary Bladder in Manipur: A Histopathological Perspective. Asian Pacific J Cancer Prev. 2012;13:2477-9.

ANNEXURE-I

ETHICAL CLEARANCE

B.L.D.E.UNIVERSITY'S
SHRI.B.M.PATIL MEDICAL COLLEGE, BIJAPUR – 586103
INSTITUTIONAL ETHICAL COMMITTEE

No/58/2015
20/11/15

INSTITUTIONAL ETHICAL CLEARANCE CERTIFICATE

The Ethical Committee of this college met on 17-11-2015 *at* 03 pm *scrutinize the Synopsis of Postgraduate Students of this college from Ethical Clearance point of view. After scrutiny the following original/corrected and revised version synopsis of the Thesis has accorded Ethical Clearance.*

Title "A Study on Histopathological spectrum of lesions in urinary bladder biopsies"

Name of P.G. Student : Dr. S. Sucmitha
Dept of Pathology

Name of Guide/Co-investigator : Dr. Girija.s patil, Assoc prof

DR.TEJASWINI VALLABHA
CHAIRMAN

CHAIRMAN
Institutional Ethical Committee
BLDEU's Shri B.M. Patil
Medical College,BIJAPUR-586103.

Following documents were placed before E.C. for Scrutinization
1)Copy of Synopsis/Research Project
2)Copy of informed consent form.
3)Any other relevant documents.

ANNEXURE-II

BLDEUs, SHRI B.M.PATIL MEDICAL COLLEGE HOSPITAL AND RESEARCH CENTER, VIJAYAPURA- 586103

INFORMED CONSENT FORM FOR DISSERTATION/RESEARCH

I, the undersigned,_____ , S/O D/O W/O _____, aged ____years, ordinarily resident of _____ do hereby state/declare that Dr _____ of _____ Hospital has examined me thoroughly on _____ at _____ (place) and it has been explained to me in my own language that I am suffering from _____ disease (condition) and this disease/condition mimic following diseases .

Further Doctor S Susmitha informed me that he/she is conducting dissertation/research titled A study on histopathological spectrum of lesions in urinary bladder biopsies under the guidance of Dr Girija S Patilrequesting my participation in the study. Apart from routine treatment procedure, the pre-operative, operative, post-operative and follow-up observations will be utilized for the study as reference data.

The Doctor has also informed me that information given by me, observations made/ photographs/ video graphs taken upon me by the investigator will be kept secret and not assessed by the person other than me or my legal hirer except for academic purposes.

Doctor has also informed me that during conduct of this procedure like adverse results may be encountered. Among the above complications most of them are treatable but are not anticipated hence there is chance of aggravation of my condition and in rare circumstances it may prove fatal in spite of anticipated diagnosis and best treatment made available. Further Doctor has informed me that my participation in this study help in evaluation of the results of the study which is useful reference to treatment of

other similar cases in near future, and also I may be benefited in getting relieved of suffering or cure of the disease I am suffering.

The Doctor did inform me that though my participation is purely voluntary, based on information given by me, I can ask any clarification during the course of treatment / study related to diagnosis, procedure of treatment, result of treatment or prognosis. At the same time I have been informed that I can withdraw from my participation in this study at any time if I want or the investigator can terminate me from the study at any time from the study but not the procedure of treatment and follow-up unless I request to be discharged.

After understanding the nature of dissertation or research, diagnosis made, mode of treatment, I the undersigned Shri/Smt _____ under my full conscious state of mind agree to participate in the said research/dissertation.

Signature of patient:

Signature of doctor:

Witness: 1.

2.

Date:

Place

ANNEXURE III

PROFORMA FOR STUDY

Demographic Details:

NAME:

AGE:

SEX: M/F

OCCUPATION:

RESIDENCE:

OPD / IPD no.:

Lab no./Ward no.:

Chief complaints:

History of presenting illness:

Past history:

History of intake of drugs:

Family history:

General physical examination:

Pallor :Icterus :

Built:Nourishment :

Vitals:-

Pulse :

Temp :

BP :

RR:

Weight :

Systemic examination:

Cardiovascular system

Respiratory system

Central Nervous System

Per abdomen

Clinical diagnosis:

Investigations:

Radiological:

USG-

X-RAY-

CT-

IVU-

URINE:

CULTURE SENSITIVITY:

URINE CYTOLOGY:

Histopathological diagnosis:

KEY TO MASTER CHART

HPE no	Histopathology examination number
BB	Bladder biopsy
TURBT	Transurethral resection of bladder tumor
CA	Carcinoma
TCC	Transitional cell carcinoma
SCC	Squamous cell carcinoma
HPD	Histopathological diagnosis
M	Male
F	Female
NI	Non-invasive
LP	Invasion up to lamina propria
MP	Invasion up to muscularis propria

MASTER CHART

Sl no	Age	Sex	HPE no.	Specimen	Clinical diagnosis	HPD	Extent of invasion
1	44	F	6584/15	BB	Koch's cystitis	Granulomatous cystitis	
2	45	F	6978/15	TURBT	CA Bladder	High grade papillary urothelial carcinoma	MP
3	16	M	7024/15	BB	Cystitis	Chronic nonspecific cystitis	
4	60	M	7364/15	TURBT	CA Bladder	High grade invasive urothelial carcinoma	LP
5	54	M	7465/15	TURBT	TCC- bladder	Nonpapillary invasive urothelial carcinoma	LP
6	64	M	63/16	BB	Cystitis	Chronic nonspecific cystitis	
7	75	M	1213/16	TURBT	CA Bladder	Invasive papillary urothelial carcinoma	LP
8	72	M	1217/16	TURBT	CA Bladder	Invasive nonpapillary urothelial carcinoma	MP
9	78	M	1327/16	BB	Koch's cystitis	Follicular cystitis	
10	66	F	1350/16	TURBT	CA Bladder	Low grade papillary urothelial carcinoma	LP

Sl no	Age	Sex	HPE no.	Specimen	Clinical diagnosis	HPD	Extent of invasion
11	58	M	1460/16	TURBT	CA Bladder	High grade invasive urothelial carcinoma	MP
12	37	F	1583/16	BB	Cystitis	Chronic nonspecific cystitis	
13	50	M	1624/16	TURBT	TCC	Invasive urothelial carcinoma- Clear cell variant	MP
14	19	F	1756/16	BB	Cystitis	Polypoidal cystitis	
15	36	M	2196/16	BB	Cystitis	Cystitis glandularis	
16	80	F	2378/16	TURBT	Recurrent CA bladder	High grade invasive papillary urothelial carcinoma	LP
17	55	M	2857/16	TURBT	CA Bladder	Papillary urothelial neoplasm of low malignant potential	NI
18	75	F	3055/16	TURBT	TCC	Papillary urothelial neoplasm of low malignant potential	NI
19	51	F	3408/16	BB	TCC	Chronic nonspecific cystitis	
20	75	M	3512/16	BB	Cystitis	Acute on chronic nonspecific cystitis	

Sl no	Age	Sex	HPE no.	Specimen	Clinical diagnosis	HPD	Extent of invasion
21	44	M	3552/16	BB	Koch's cystitis	Chronic non-specific cystitis	
22	65	M	3553/16	TURBT	SCC- bladder	Invasive urothelial carcinoma-Sarcomatoid variant	MP
23	65	M	3608/16	TURBT	CA Bladder	Low grade papillary invasive urothelial carcinoma	LP
24	75	M	3640/16	TURBT	CA Bladder	High grade non-invasive urothelial carcinoma	NI
25	65	M	4584/16	TURBT	CA Bladder	Low grade papillary urothelial carcinoma	NI
26	75	M	4909/16	TURBT	CA Bladder	Noninvasive low grade papillary urothelial carcinoma	NI
27	38	F	6119/16	BB	Koch's cystitis	Eosinophilic cystitis	
28	60	M	6228/16	TURBT	CA Bladder	Invasive urothelial carcinoma- glandular differentiation	MP
29	55	F	6769/16	BB	Chronic cystitis	Chronic nonspecific cystitis	

Sl no	Age	Sex	HPE no.	Specimen	Clinical diagnosis	HPD	Extent of invasion
30	65	F	7416/16	TURBT	CA Bladder	Low grade noninvasive papillary urothelial carcinoma	NI
31	60	F	7420/16	TURBT	CA Bladder	Papillary urothelial neoplasm of low malignant potential	NI
32	65	F	7647/16	BB	Focal cystitis	Chronic nonspecific cystitis	
33	70	M	8123/16	TURBT	CA Bladder	Low grade papillary urothelial carcinoma	NI
34	70	F	8150/16	TURBT	CA Bladder	High grade non invasive papillary urothelial carcinoma	NI
35	65	F	439/17	BB	Bladder calculi	Chronic nonspecific cystitis	
36	64	M	589/17	TURBT	CA Bladder	Papillary urothelial neoplasm of low malignant potential	NI
37	45	F	1413/17	BB	Koch’s cystitis	Chronic nonspecific cystitis	
38	2	M	1440/17	BB	Bladder neck polyp	Fibroepithelial polyp	

Sl no	Age	Sex	HPE no.	Specimen	Clinical diagnosis	HPD	Extent of invasion
39	73	M	1500/17	TURBT	CA Bladder	Invasive high grade urothelial carcinoma	MP
40	65	M	1553/17	BB	Koch's cystitis	Chronic nonspecific cystitis	
41	59	M	2503/17	BB	Chronic cystitis	Chronic nonspecific cystitis	
42	36	F	2649/17	BB	Koch's cystitis	Chronic nonspecific cystitis	
43	65	F	3134/17	BB	Koch's cystitis	Cystitis cystica	
44	67	M	3262/17	TURBT	CA Bladder	Low grade papillary non-invasive urothelial carcinoma	NI
45	75	M	4195/17	TURBT	CA Bladder	High grade invasive urothelial carcinoma	LP
46	58	M	5460/17	TURBT	TCC bladder	Invasive urothelial carcinoma	MP
47	65	M	5794/17	TURBT	CA Bladder	Invasive urothelial carcinoma- high grade	MP
48	55	F	5900/17	TURBT	CA Bladder	Invasive urothelial carcinoma-Squamous differentiation	MP